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EDITOR
MAURICE CAMPBELL
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WILLIAM WITHERING*

BY

K. D. WILKINSON

From the Birmingham General Hospital

William Withering was descended from a long line of yeoman farmers who lived in the parish of Checkley in Staffordshire. An ancestor had married an heiress from Chipnall in Shropshire and had migrated in the reign of Charles I, but Edmund Withering, who practised as an apothecary at Wellington from 1738 to 1769, was the first instance of any medical association in the family. He married the sister of Dr. Brooke Hector of Lichfield, and his son William was born in 1741. William was destined for the profession of medicine from his earliest days; he was educated at home, apprenticed to his father, and went to Edinburgh as a student at the age of 21 years. Edinburgh was a great medical school even then, with upwards of 200 students in each year, but only a small proportion took the M.D. degree. At Edinburgh Withering learned to play various musical instruments and golf; he became a proficient draughtsman and a fluent speaker and writer. He wrote his M.D. thesis on malignant putrid sore throat and took his degree in July, 1766. In Edinburgh he made a number of lifelong friends and acquired a scientific outlook which enabled him to distinguish himself in chemistry, in botany, and in medicine.

Early in 1767 he settled in practice in Stafford, was appointed physician to the recently established Stafford Infirmary, and made a new set of friends. In November, 1769, his father, Edmund, died and left him all his freehold property subject to annuities to his mother and sisters, and three years later he married and began to feel that his professional income was inadequate, for he never made £100 a year while in Stafford. It was there that he wrote his botanical arrangement, a carefully prepared detailed work in English for English students, based on the Linnæan system. In the preface to the first edition of the botany he wrote, " The author will thankfully receive any communication that can tend to render this book more perfect and in case the public ever call for a second edition such new facts or observations as occur shall be inserted with suitable acknowledgements."

He also wrote, " Many people will be surprised to find so little said upon the medicinal virtues of plants, but those who are best enabled to judge of this matter will perhaps think that the greater part of that little might well have been omitted. . . . The dreadful apprehension that men formerly entertained of poisons made them fearful of employing substances that were capable of doing mischief, and they therefore rejected those that were most likely to do good. . . . We shall sooner attain the end proposed if we take up the subject as altogether new, and, rejecting the fables of the ancient herbalist, build only upon the basis of accurate and well considered experiments."

It is difficult to compare Withering's book with its contemporaries: it was better written than most and outlasted all. Withering himself produced three editions, with great industry during ill health and busy practice, his son edited a further four, and the final edition, the fourteenth, appeared in 1877, one hundred and one years after the original publication.

In February 1775 Dr. William Small of Birmingham died, and Dr. Erasmus Darwin wrote to

" Dr. William Withering, Physician at Stafford
" from Lichfield on 25th February, 1775

" DEAR DOCTOR,

I am at this moment returning from a melancholy scene, the death of a friend who was most dear to me, Dr. Small of Birmingham, whose strength of reasoning, quickness of intellect, learning

* This article is part of the St. Cyres lecture delivered at the National Heart Hospital on Wednesday, June 15, 1949. A book on William Withering by K. D. Wilkinson is due to be published shortly by Wright of Bristol.

in the discoveries of other men, and integrity of heart (which is worth them all) had no equal. Mr. Boulton suffers an inconceivable loss from the doctor's mechanical as well as medical ability. . . . Now it occurred to me that if you should choose that situation your philosophical taste would give you the friendship of Mr. Boulton which would operate all that for you which it did for Dr. Small. I saw by his papers that he gained about £500 a year at an average. . . . I shall not mention having wrote this letter to you but shall be glad of a line in answer, and please put private on the internal cover.

Adieu,

E. DARWIN"

FIG. 1.—The General Hospital near Birmingham. Opened in 1779, the physicians being Dr. John Ash, Dr. William Withering, Dr. Smith, and Dr. Edward Johnston.

So Withering came to Birmingham in May 1775, lodged with Mr. Wheeley at No. 10, The Square, and took over Dr. Small's consulting-room at No. 9, Temple Row. But each week he drove back to Stafford to see his patients at the Infirmary—30 miles each way. Withering was only 34, yet he had attracted Dr. Darwin's notice; perhaps he met him while staying in Lichfield with his uncle Dr. Brooke Hector.

Before the establishment of a hospital in Birmingham the physicians used to see at their consulting-rooms without fee the sick poor of the city for one or two hours a day. Dr. Small had done this; Dr. Withering continued the practice and saw between two and three thousand persons a year. It was upon some of these that the digitalis was first tried.

In 1775 he was asked about a family receipt for the cure of the dropsy, and was told that it had been kept as a family secret for many years by an old Shropshire woman who had sometimes made

cures when more regular practitioners had failed. The medicine contained twenty different herbs and was said to produce vomiting and purging. Withering said that it was not difficult for one conversant in these subjects to perceive that the active plant could be none other than the foxglove. It is startling to learn that a botanist in 1775 knew enough pharmacology to detect the active ingredient in a herb tea. He tried it out on his free patients, and was especially encouraged when Dr. John Ash told him that Dr. Crawley, principal of Brazen Nose College, had been cured of a hydrops pectoris by digitalis root, but as a biennial plant is unlikely to have a uniformly active root Withering used the leaves and gathered them when the plant was in flower, because he found that they varied in dose if gathered at other seasons. Then he dried the leaf and found it was five times as potent as the fresh leaf. At first he used a decoction, but in order to obtain more accurate dosage turned to an infusion and finally preferred the dried leaf.

In 1785, after using the medicine for ten years, he published his *Account of the Foxglove*. It was a small book of 207 pages with a delightful coloured frontispiece from the Flora Londinensis. Withering recorded all the 163 cases in which he had prescribed the foxglove; letters from correspondents describe a further 55 cases. Dr. Cawley, brother of the late Principal of Braze Nose, wrote details of his brother's illness and treatment, and Withering calculated that each dose the Principal took had been at least twelve times what a strong man should have taken, and concluded that either Dr. Cawley was remarkably retentive of life or that the root must have been particularly inactive. " Shall we wonder," he wrote, " that patients refuse to repeat such a medicine and that practitioners tremble to prescribe it ? " The book was printed by Miles Swinney of Birmingham and cost five shillings. The preface is interesting and shows his scientific approach to the question:

" After having been frequently urged to write upon this subject, and as often declined to do so, from apprehension of my own inability, I am at length compelled to take up my pen, however unqualified I may still feel myself for the task.

" The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficiency should be condemned and rejected as dangerous and unmanageable.

" It is now about ten years since I first began to use this medicine. Experience and cautious attention gradually taught me how to use it. For the last two years I have not had occasion to alter the modes of management: but I am still far from thinking them perfect.

" It would have been an easy task to have given select cases, whose successful treatment would have spoken strongly in favour of the medicine, and perhaps been flattering to my own reputation. But Truth and Science would condemn the procedure. I have, therefore, mentioned every case in which I have prescribed the Foxglove, proper or improper, successful or otherwise. Such a conduct will lay me open to the censure of those who are disposed to censure, but it will meet the approbation of others, who are the best qualified to be judges.

" To the Surgeons and Apothecaries with whom I am connected in practice, both in this town and at a distance, I beg leave to make this public acknowledgement, for the assistance they so readily afforded me.

" The cases related from my own experience are generally written in the shortest form I could contrive, in order to save time and labour; but the cases communicated by other practitioners, are given in their own words. I must caution the reader, who is not a practitioner in physic, that no general deductions, decisive upon the failure or success of the medicine, can be drawn from the cases I now present to him. These cases must be considered as the most hopeless and deplorable that exist; for physicians are seldom consulted in chronic diseases, till the usual remedies have failed: and, indeed, for some years, whilst I was less expert in the management of the Digitalis, I seldom prescribed it, but when the failure of every other method compelled me to do it; so that upon the whole, the instances I am going to adduce, may truly be considered as cases lost to the common run of practice, and only snatched from destruction, by the efficiency of

the Digitalis; and this in so remarkable a manner, that, if the properties of that plant had not been discovered, by far the greater part of these patients must have died.

" There are men who will hardly admit of any thing which an author advances in support of a favourite medicine, and I allow they may have some cause for their hesitation; nor do I expect they will waive their usual modes of judging upon the present occasion. I could wish, therefore, that such readers would pass over what I have said, and attend only to the communications from correspondents, because they cannot be supposed to possess any unjust predilection in favour of the medicine: but I cannot advise them to this step, for I am certain they would then close the book, with much higher notions of the efficacy of the plant than they would have learnt from me. Not that I want faith in the discernment or in the veracity of my correspondents, for they are men of established reputation; but the cases they have sent me are, with some exceptions, too much selected. They are not upon this account less valuable in themselves, but they are not the proper premises from which to draw permanent conclusions. I wish the reader to keep in view, that it is not my intention merely to introduce a new diuretic to his acquaintance, but one which, though not infallible, I believe to be much more certain than any other in present use. After all, in spite of opinion prejudice, or error, TIME will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind."

Birmingham.
1*st July* 1785.

Dr. Hope, Dr. Duncan, and other Edinburgh physicians had been told by Dr. Jonathan Stokes and Mr. Charles Darwin—eldest son of Erasmus Darwin—of the use of digitalis, but all gave too large doses. Withering's fourth case is important.

In June 1776 a married lady, between 40 and 50 years of age, was attacked by a severe cold shivering fit, succeeded by a fever, great pain in her left side, shortness of breath, perpetual cough, and after some days, copious expectoration:

" . . . on the 4th June Dr. Darwin (then resident at Lichfield) was called to her and gave her various medicines.

" On the 25th July I was desired to meet Dr. Darwin at the lady's house. I found her nearly in a state of suffocation; her pulse extremely weak and irregular, her breath very short and laborious, her countenance sunk, her arms of a leaden colour, clammy and cold. She could not lie down in bed and had neither strength nor appetite, but was extremely thirsty. Her stomach, legs, and thighs, were greatly swollen; her urine very small in quantity. She had experienced no relief from any means that had been used. In this situation I knew of nothing likely to avail us, except Digitalis: and accordingly I proposed the Digitalis to be tried; adding, that I sometimes had found it to succeed when other, even most judicious methods, had failed. Dr. Darwin very politely acceded immediately to my proposition, and, as he had never seen it given, left the preparation and the dose to my direction. The patient took five draughts, which made her very sick and acted very powerfully upon the kidneys, for within the first twenty-four hours she made upwards of eight quarters of water. The sense of fullness and oppression across her stomach was greatly diminished, her breath was eased, her pulse became more full and more regular, and the swellings of her legs subsided.

" It is now almost nine years since the Digitalis was first prescribed for this lady, and notwithstanding I have tried every preventive method I could devise, the dropsy still continued to recur at times; but is never allowed to increase so as to cause much distress, for she occasionally takes the infusion and relieves herself whenever she chooses. Since the first exhibition of that medicine, very small doses have been always found sufficient to promote the flow of urine. I I have been more particular in the narrative of this case, partly because Dr. Darwin has related it rather imperfectly in the notes to his son's posthumous publication, trusting, I imagine, to

memory, and partly because it was a case which gave rise to a very general use of the medicine in that part of Shropshire."

After enumerating all the cases Withering summarized his opinion of Digitalis under the heading *Effects, Rules and Cautions.*

" The Foxglove, when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death. (I am doubtful whether it does not sometimes excite a copious flow of saliva.)

" When given in a less violent manner, it produces most of these effects in a lower degree; and it is curious to observe that the sickness, with a certain dose of medicine, does not take place for many hours after its exhibition has been discontinued; that the flow of urine will often precede, sometimes accompany, frequently follow the sickness at the distance of some days, and not unfrequently be checked by it. Let the medicine, therefore, be given in the doses described:—let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowel; let it be stopped upon the first appearance of any one of these effects, and I will maintain that the patient will not suffer from its exhibition, nor the practitioner be disappointed in any reasonable expectation.

" If it purges, it seldom succeeds well."

He then made a series of most important clinical observations under the title *Constitution of Patients.*

" Independent of the degree of disease, or of the strength or age of the patient, I have had occasion to remark, that there are certain constitutions favourable, and others unfavourable to the success of the Digitalis. From large experience, and attentive observation, I am pretty well enabled to decide ' a priori ' upon this matter, and I wish to enable others to do the same: but I feel myself hardly equal to the undertaking. The following hints, however, aiding a degree of experience in others, may lead them to accomplish what I yet can describe but imperfectly.

" It seldom succeeds in men of great natural strength, of tense fibre, of warm skin, of florid complexion, or in those with a tight and cordy pulse.

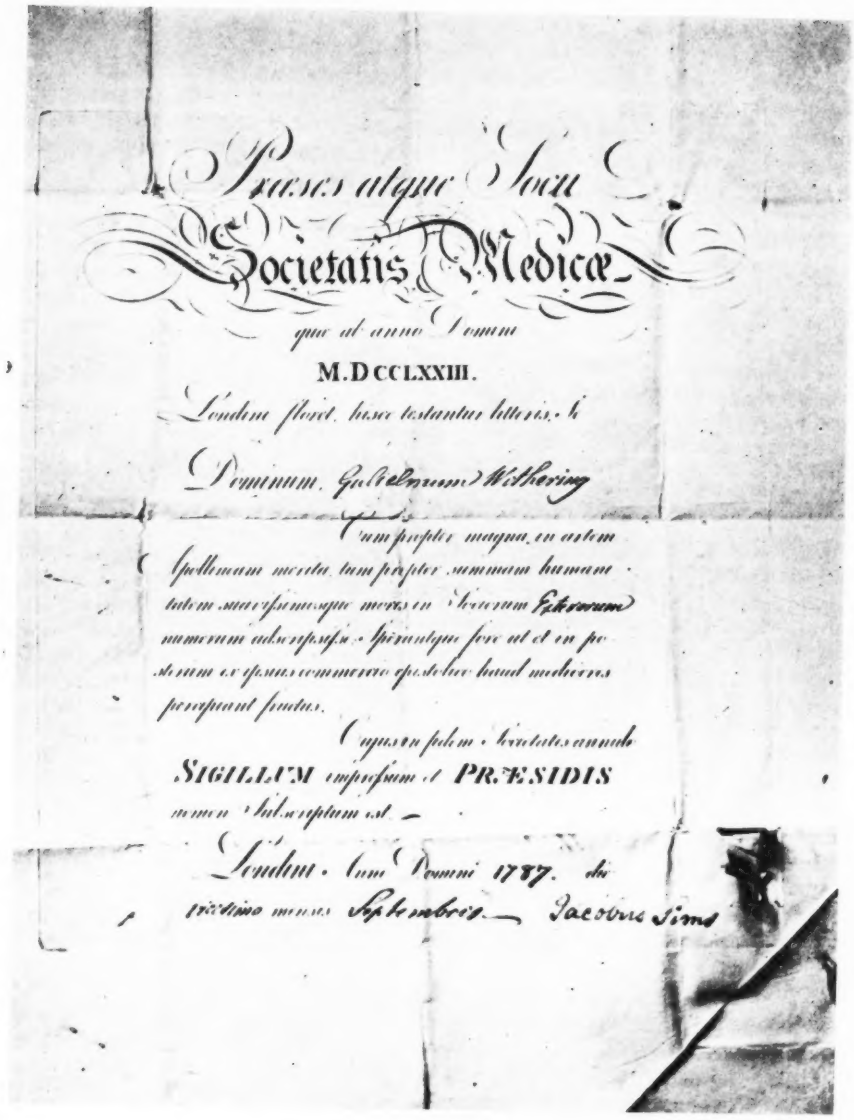
" If the belly in ascites be tense, hard and circumscribed, or the limbs in anasarca solid and resisting, we have but little hope.

" On the contrary, if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcous limbs readily pitting under the pressure of the finger, we may expect the diuretic effects to follow in a kindly manner. In cases which foil every attempt at relief, I have been aiming, for some time past, to make such a change in the constitution of the patient, as might give a chance of success to the Digitalis."

In 1787 Withering was made a member—the first provincial member—of the London Medical Society (Fig. 2).

Withering was not only a botanist and a physician; he was a chemist of ability and accomplishment. In 1782 he presented a paper on the chemical analysis of the Ragstone and Toadstone to the Royal Society. Two years later he communicated his experiments and observations on Terra Ponderosa and recognized the carbonate of barium as distinct from barytes. He suggested that barium salts were a good test for sulphates or sulphuric acid.

In 1785 he translated Professor Bergman's textbook on chemistry under the title of *Outlines of Mineralogy* for Mr. Matthew Boulton; many years before he had translated Professor Bergman's book on water analysis into English. It was in 1793 while in Portugal that he analysed the famous Queensbath, a hot sulphur spring some 60 miles north of Lisbon, and this achievement was signalized by his election to the membership of the Portuguese Academy of Science. He made nitrate of


Societatis Medicæ

M.DCCLXXIII.

Londini floret, hasce testantur litteris, D.

Dominum Gulielmum Withering

SIGILLUM impressum et PRÆSIDIS

Londini, Anno Domini 1787, die

vicesimo mensis Septembris. Jacobus Sims

FIG. 2.—The diploma of the London Medical Society making Dr. William Withering a Member—the first provincial member—on September 20, 1787. Sent by Dr. J. C. Lettsom.

mercury so as to be able to give an exact dose in the treatment of syphilis, and no doubt he took a lively interest in the chemical discussions at the meetings of the Lunar Society.

Withering wrote long letters expounding chemical knowledge to Lady Catherine Wright, and discussed the decomposition of water and the principles of acidity with Priestley, the composition of urinary calculi and the treatment of pulmonary disease by the inhalation of gases. At a Lunar Society meeting he even read a poem on the life and death of Phlogiston: Priestley believed in the Phlogiston theory; Withering did not.

In 1786 he took a 14 years' lease of Edgbaston Hall, at the very large annual rental of two hundred and thirty seven pounds ten shillings, where he bred Alderneys and Newfoundland dogs and by skilled management made a profit on the estate. (A picture of the Hall appeared in this journal in volume II, page 299, in October 1940). In 1791 there were most serious riots in Birmingham in which many large houses were attacked and damaged or destroyed. Edgbaston Hall was attacked but was fortunate to escape serious damage. The disturbance was fomented by rival religious factions who distrusted Dr. Joseph Priestley and his friends for their outspoken approval of the French Revolution. It was at Edgbaston Hall that Withering entertained many of the leading scientists and botanists of his time, for he had a European reputation, and there too the Lunar Society met.

In the eighteenth century, when books were scarce and expensive and technical journals quite unknown, men of similar interests began to form societies for friendship and the interchange of ideas. The Royal Society in London was the best known and the earliest, but there were many provincial bodies with similar constitutions, and among these the Birmingham Lunar Society was the most brilliant. It was started about the year 1765 by Matthew Boulton, the great Birmingham industrialist, Erasmus Darwin, the scientific physician and botanical poet of Lichfield, and William Small, physician and consultant chemist to Matthew Boulton. The meetings were held each month at the houses of the various members to dine and discuss. They took their name because the meetings were held at the full moon so as to facilitate the drive home through the unlighted streets—important since Darwin and Wedgwood had long journeys to make. The Lunar Society kept no records and had neither a secretary nor minutes; it is, therefore, quite impossible to determine the names or dates of its various members or the subjects discussed. We know that chemical experiments, the weather, inventions of all sorts, conjuring demonstrations, and literary discussions had a place at the meetings, and that various mechanical developments were demonstrated from time to time and that many of its members became famous.

James Watt and Withering joined the society in 1775 after the death of Dr. Small, and Joseph Priestley became a member about 1780 when he came to Birmingham.

On April 5, 1778, Erasmus Darwin wrote:

> " DEAR BOULTON,
>
> I am sorry that the infernal divinities who visit mankind with diseases and are therefore at perpetual war with doctors should have prevented my seeing all your great men at Soho today. Lord! What inventions, what wit, what rhetoric metaphysical, mechanical and pyrotechnical will be on the wing, bandied like a shuttlecock from one to another of your troop of philosophers! While poor I, I by myself, imprisoned in a postchaise am joggled and jostled and bumped and bruised along the King's high-road, to make war upon a stomach-ache or a fever! "

James Watt was the engineer whose life interest was steam; he became Boulton's partner and a pioneer in the research into the composition of water.

Withering had a big practice; in 1780 he earned over 2000 guineas, travelling long distances through the Midlands and into Wales. In one year he travelled over 6000 miles. He had a carriage accident in 1781 and sustained a fractured collar-bone and some concussion, but continued his work, within four days driving out 20 miles to see an apothecary's wife.

It was in 1776, one year after he reached Birmingham, that he developed a curious fever. In

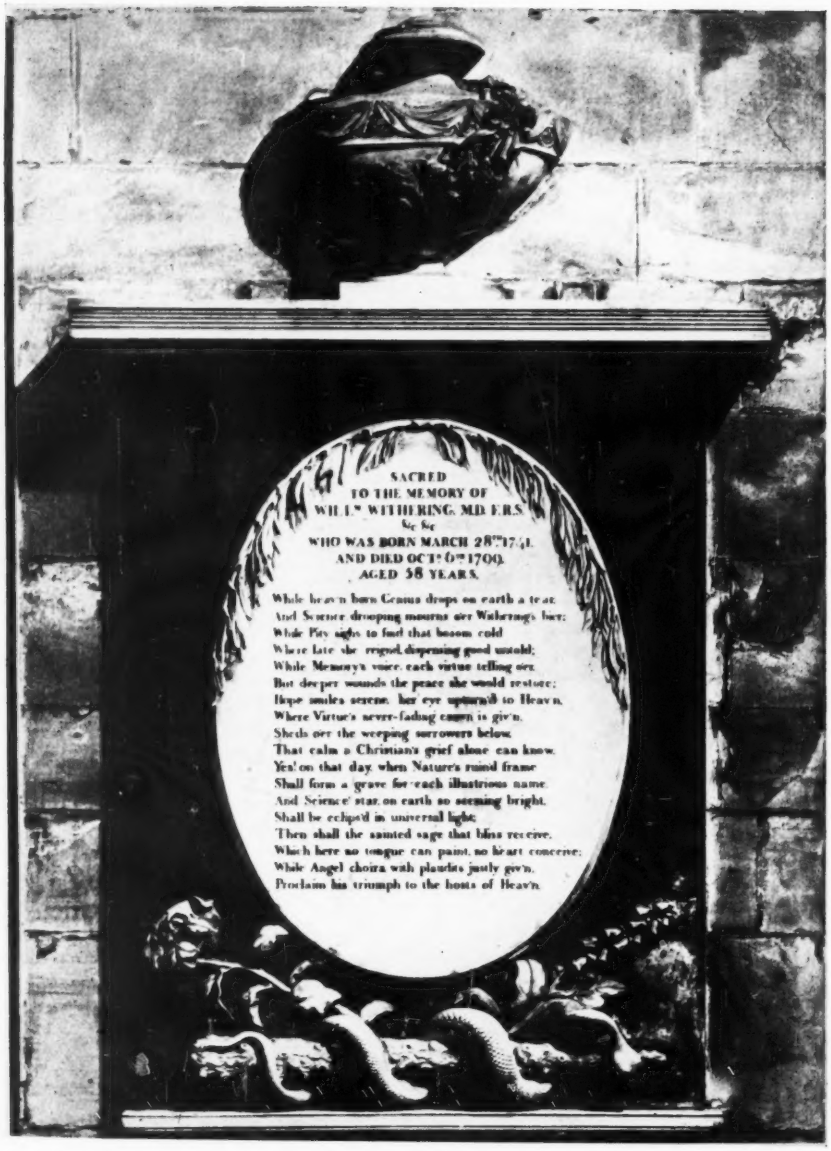

SACRED
TO THE MEMORY OF
WILL.M WITHERING, M.D. F.R.S.
&c &c
WHO WAS BORN MARCH 28TH 1741.
AND DIED OCT.R 6TH 1799.
AGED 58 YEARS.
While heav'n born Genius drops on earth a tear
And Science drooping mourns o'er Witherng's bier;
While Pity sighs to find that bosom cold
Where late she reign'd, dispensing good untold;
While Memory's voice, each virtue telling o'er
But deeper wounds the peace she would restore;
Hope smiles serene, her eye upturn'd to Heav'n,
Where Virtue's never-fading crown is giv'n,
Sheds o'er the weeping sorrowers below
That calm a Christian's grief alone can know.
Yes! on that day, when Nature's ruin'd frame
Shall form a grave for each illustrious name,
And Science' star, on earth so seeming bright,
Shall be eclips'd in universal light,
Then shall the sainted sage that bliss receive,
Which here no tongue can paint, no heart conceive;
While Angel choirs with plaudits justly giv'n,
Proclaim his triumph to the hosts of Heav'n.

FIG. 3.—The Memorial Tablet erected to the memory of Dr. William Withering by his son. Designed by W. Hollins.

the spring he was seized with an irregular fever which lasted three weeks and prevented him from doing or even thinking of anything that could be avoided.

From this time slowly but steadily his physical health deteriorated and he suffered from repeated attacks of pneumonia, pleurisy, hæmoptysis, and fever. In time Withering recognized that he was the victim of a progressive disease—whether this was bronchiectasis or tuberculosis must remain uncertain. Boulton and Watt installed a ventilating system at Edgbaston Hall so as to maintain a constant temperature and humidity. In 1792 his health forced him to resign from the staff of the General Hospital, and he wintered in Portugal for two years but did not gain any great benefit from the experiment and preferred his air-conditioned home at Edgbaston, where he could continue his domestic employments—the third edition of the Botany, a correspondence with numerous friends, and the entertainment of visitors, for Withering was now possessed of a Continental reputation as a botanist, a physician, and a philosopher. When he could no longer practise medicine he had more time to devote to botany and his other hobbies and experiments in breeding and the cultivation of his estate at Edgbaston. So the years passed with repeated attacks of pleurisy and hæmoptysis, and periodic recovery. Then in 1799 he decided to move to a smaller house on the south side of the town; having supervised the details of the necessary reconstruction all the summer, he moved in September. But the move and the illness of his wife were too much for his feeble body, and on Sunday, October 6, 1799, he died. His funeral at Edgbaston Old Church was attended by a large congregation, with Established and Dissenting Clergy officially present, a rare event at that date. And a friend wrote that the flower of English botany was Withering.

CORONARY INVOLVEMENT IN DISSECTING ANEURYSM OF THE AORTA

BY

SAMUEL ORAM AND MARY C. HOLT

From the Cardiological Department King's College Hospital

Received June 5, 1949

Although there are many reports of cases of dissecting aneurysm of the aorta, the number with involvement of the coronary arteries, either deduced from electrocardiographic change or discovered at death, is not great. Shennan (1934) makes no mention of these in his monograph. Also, in the few examples that have been recorded, little attention has been paid to the exact mode of interference with the coronary blood supply. The problem is not without clinical interest, as cases of dissecting aortic aneurysm with long survival are well known. Graham (1886) is usually considered to have recorded the longest period of survival, his patient living for more than thirty years; but the date of formation of the aneurysm is assumed by him to be that on which an internal injury was sustained. Even after involvement of the coronary arteries the patient may survive for many months.

From a study of the autopsy reports it is apparent that there are several ways in which the coronary blood supply can be rendered inadequate. First, the coronary arteries can be involved in the aortic dissection, which may merely occlude their mouths, or actually extend into and along their walls. Secondly, they can be compressed, either by extravasated blood from the leaking aneurysm, or by the blood of a hæmopericardium. It has been claimed that this blood may distend the pericardial sac, thereby compressing the coronary arteries, or give rise to the formation of pericardial adhesions which subsequently exert traction. Thirdly, cases are recorded with cardiographic changes of the type met with in coronary ischæmia, yet without obvious involvement of the coronary arteries. These changes have been considered to result from deficient coronary filling, due to the fall in blood pressure associated with massive hæmorrhage from the dissecting aneurysm. Finally, because atheroma is common in patients with dissecting aneurysm, it is also to be expected that coronary occlusion will, at times, be an incidental event independent of the dissection.

We record below a case showing cardiographic changes in which both coronary arteries were surrounded by extravasated blood derived from the aneurysm.

Case Report

On the morning of 24/12/48 the patient, a man aged 73, was bending to fasten his shoe when he was seized by a stabbing substernal pain of great severity. This radiated to the lower jaw, through to the back, and down as far as the lumbar region, and across the upper abdomen. The arms were unaffected. This distribution of the pain suggested the presence of a dissecting aortic aneurysm. Sweating and dyspnœa accompanied the pain, which persisted until morphia was administered two hours later. Soon after the onset the patient coughed up about a teaspoonful of fresh blood, and thereafter the sputum was streaked with blood. Vomiting occurred at intervals throughout that day.

By late the same evening he was restless, pale, slightly cyanosed, and sweating. The pulse rate was 86, the rhythm regular, and the volume poor. No difference could be detected between the

radial pulses or the femoral pulses. The blood pressure was 95/65 in both arms and there were no signs of congestive failure. The cardiac impulse was impalpable. On auscultation a soft basal systolic murmur was present, but no diastolic murmur or added sounds were heard. Cheyne-Stoke's respiration was accompanied by scattered rhonchi throughout both lungs. Nothing abnormal was found in the abdomen or the central nervous system.

For one year prior to this incident the patient had been aware of increasing dyspnœa on exertion, but had experienced no pain. The family history yielded no relevant information.

On 25/12/48 he was admitted to hospital. By that time he complained only of substernal discomfort, with a sensation of numbness in both arms. An electrocardiogram (Fig. 1) was taken the same day. Standard lead I showed a Q wave of one millimetre depth and slight RS–T segment elevation (less than one millimetre) with inversion of the T wave (minus 1·5 millimetres), there being corresponding slight RS–T segment depression in leads II and III, which also showed some slurring of the QRS complexes. Leads VL and VF closely resembled standard leads I and III respectively. The unipolar chest leads V2 to V6 showed elevation of the junction and RS–T segment, the maximum deviation of the junction being 4·5 millimetres in V3 and V4; the T waves were biphasic (±) in V3 to V6, the inversion being greatest in leads V5 and V6; Q waves were absent throughout. No digitalis or other drug likely to affect the T waves had been administered.

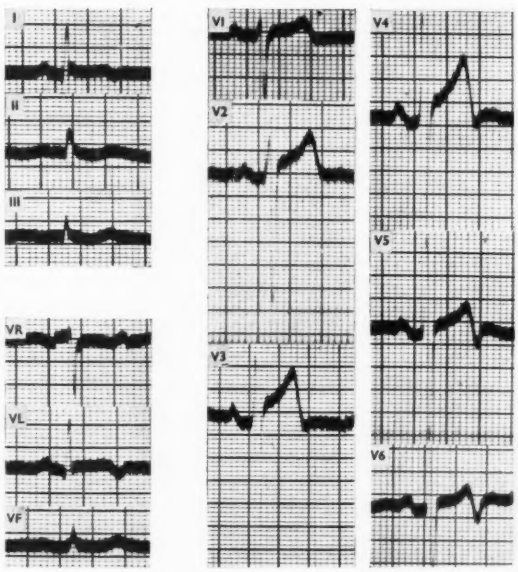


FIG. 1.—Cardiogram showing inversion of the T wave in leads I and VL; elevation of the junction and RS–T segment, and biphasic T waves in leads V3 to V6. The Q waves in leads I and VL are normal and no Q waves are present in the chest leads.

FIG. 2.—Skiagram showing the presence of a large rounded supracardiac shadow which has spread out on each side to obscure the lung apices.

No further pain occurred after admission. The next day the blood pressure had risen to 150/80, and cyanosis and dyspnœa were less evident, but examination of the lungs revealed fine rales at the right base. A portable X-ray of the chest on 26/12/48 (Fig. 2) showed the presence of a large, rounded supracardiac shadow, which had spread out on each side along the line of the first rib to obscure both lung apices. Within the mediastinal shadow, on the left side, a calcified semi-circle was visible, corresponding to the position of the aortic knob. The leucocyte count on 26/12/48

was 82,000 per cubic millimetre, of which 81 per cent were polymorphonuclear. On 27/12/48 the patient was drowsy, and moist sounds were heard in all areas of both lungs. Steady deterioration in his condition followed, and he died later that day.

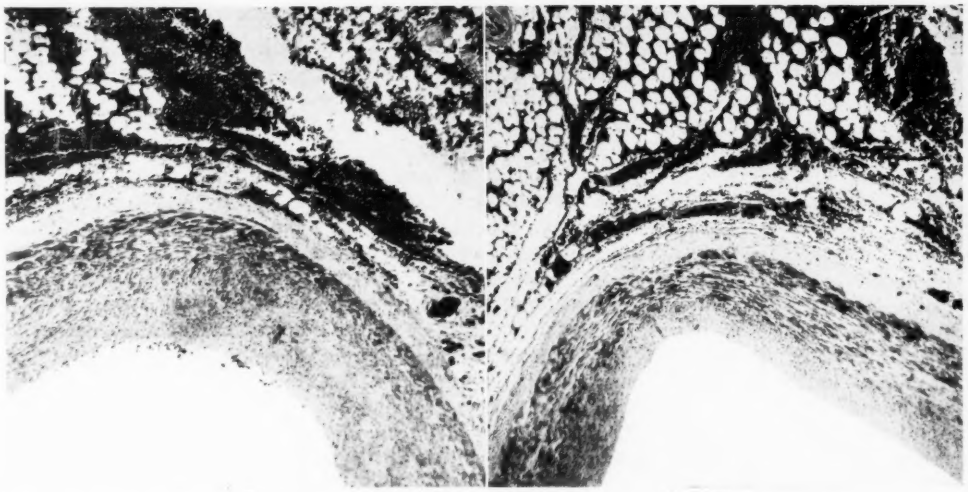
Necropsy was performed twelve hours after death and showed a dissecting aneurysm of the aorta with hæmopericardium, and primary hypertension with a terminal malignant phase. The aorta was moderately atheromatous. A horizontal tear, 4·5 cm. long, in the aortic arch just posterior to the left subclavian orifice, led into a blood-filled cavity along the right border of the ascending aorta.

FIG. 3.—The specimen shows involvement by dissection of the innominate, left common carotid, and left subclavian arteries. The arrow indicates the beginning of the left coronary artery which has been laid open.

Dissection of the wall of the aorta extended from its origin to the diaphragm and involved the innominate, left common carotid, and left subclavian arteries (Fig. 3). There was diffusion of blood along the wall of the left coronary artery and its anterior descending branch for a distance of 4·5 cm. from its orifice (Fig. 4), and along the right coronary artery for 5·0 cm. (Fig. 5). At the time, this appearance was thought to be due to an extension of the dissecting process along the coronary arteries themselves, but subsequent microscopic examination of both arteries showed that the blood lay outside the adventitia in the epicardial fat, the arterial coats being intact (Fig. 6).

FIG. 4.—Showing extravasation of blood around the first part of the left coronary artery, which has been laid open and is seen running vertically. A piece has been removed for section.

FIG. 5.—Showing blood surrounding the beginning of the right coronary artery, seen running horizontally.



A B

FIG. 6.—(A) Left coronary artery. (B) Right coronary artery. Blood is seen to lie outside the adventitia. The arterial coats are intact. Magnification, ×25.

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Early atheromatous changes were present in both coronary arteries, but there was no evidence of obstruction. There were about 300 ml. of fluid blood in the pericardial sac. The heart showed moderate hypertrophy of the left ventricle, but was otherwise normal. The lungs were congested and œdematous, and each pleural sac contained about 600 ml. of fluid blood. There was also extensive diffusion of blood into the mediastinum and along the fascial planes of the neck up to the level of the hyoid. The other organs appeared normal with the exception of the kidneys, which showed some narrowing of the cortex. Microscopically, foci of fibrinoid necrosis were found in the capillary loops of many of the glomeruli, and there was severe hyalinization of the arterioles with some medial thickening in the larger vessels. Scattered small areas of hæmorrhage were seen in both cortex and medulla, and some tubules contained red blood corpuscles. Arteriosclerosis was also present in the pancreas and adrenals. These changes were thought to indicate a malignant terminal phase in a previously benign hypertension.

Discussion

As mentioned above, there are several ways in which the coronary blood flow can be rendered inadequate in dissecting aneurysm. The most obvious of these, but not the commonest, is extension of the aortic dissection to involve the coronary arteries. Its rarity is probably due, as Wainwright (1944) suggested, to the fact that once the aortic ring has been reached the process is often rapidly terminated by rupture into the pericardial sac. This would also account for the paucity of cardiographic records in these cases. Even when the dissection has reached the coronary arteries it occludes their ostia alone, either one (Glendy *et al.*, 1937; Logue, 1943), or both (Zoints, 1943; Mallory, 1945, 1946, 1947), more often than it involves the coronary artery walls themselves (Pretty, 1931; Glendy *et al.*, 1937; Gardner, *et al.*, 1939; Bayley and Monte, 1943; Wainwright, 1944). In the case reported by Weiss (1938) the aortic dissection occluded both coronary ostia and, in addition, extended for one centimetre along the wall of the left coronary artery; this completely occluded its lumen and a recent infarct was found in the anterior wall of the left ventricle. Actual myocardial infarction is uncommon in these cases of dissecting aneurysm with electrocardiographic evidence of ischæmia. In the case with cardiographic change recorded by Bayley and Monte (1943) the right coronary artery was almost completely occluded by dissection, yet despite this, the myocardium was normal. In fact, the only other case showing infarction was that of Wainwright (1944) in which, again, dissection of the coronary arteries had occurred.

The cases in which interference with coronary blood flow appears to have resulted from compression by extravasated blood in the surrounding tissues fall into two groups. First, there are those in which the perivascular tissues and overlying epicardium are infiltrated by blood from the leaking aneurysm (Hamburger and Ferris, 1938; Reisinger, 1940; Niehaus and Wright, 1941; Sacks, 1945; Halliday and Robertson, 1946). Our own case belonged to this category. Blood surrounding the coronary vessels does not necessarily compress them. In our case, although both coronary arteries were surrounded, the area of ischæmia was only in the distribution of the left coronary artery, and it is possible that irritation of the vessel wall by surrounding clot may have led to spasm. Secondly, the coronary arteries may at times be compressed by a hæmopericardium. Usually, of course, this is a terminal event and the effects on the cardiogram are not seen, but in two cases (Hardaway and Green, 1935; Steiner, 1945) it was considered that a clotted hæmopericardium had caused obstruction of the left coronary artery, in the first case by pressure of the blood clot, and in the second by the formation of pericardial adhesions. We feel that it is unlikely that the degree of cardiac tamponade could be so great as to compress the coronary arteries yet permit survival of the patient. That pericardial adhesions may form after hæmorrhage into the pericardial sac, and even lead to constrictive pericarditis, is well known, but we doubt very much whether the T wave inversion in such cases is due to traction by the adhesions on the coronary arteries.

Few explanations have been offered to account for the cardiographic changes that may occur in dissecting aneurysm in the group of cases in which no obvious local lesion of the coronary

arteries is to be found. Bourne and Mills (1946) suggested that possible responsible factors were changes in tension of the aortic wall induced by hæmorrhagic infiltration, mechanical displacement of the heart, and possibly acute necrosis in the myocardium similar to the medial necrosis occurring in the aorta. In support of the last suggestion they cite a case in which the cardiogram showed RS–T segment depression in each of leads I, II, III and IV, changing to left bundle branch block on the day of death, and where focal necrosis of the myocardium was found at autopsy. We feel that this type of case must be rare. If such myocardial necrosis were common, it could scarcely have escaped attention, yet we could find only one other reported case at all similar (Mallory, 1942). Moreover, in both these cases, circumstances were such that compression of the coronary mouths by extravasated blood could have accounted for the findings. Elliot and Evans (1936) attempted to account for this group by suggesting that the cardiographic changes were the result of relative myocardial ischæmia induced by a sudden decrease in the blood volume following hæmorrhage from the aneurysm, in a heart whose coronary arteries were already thickened. In this connection it is interesting to note that we could find only 6 cases in which cardiographic change was present but the dissection was confined to regions distant from the heart, and massive hæmorrhage had occurred in every one of them (White *et al.*, 1934; Osgood *et al.*, 1936 ; Elliot and Evans, 1936; Logue, 1943; Bourne and Mills, 1946). However, it is unusual for severe hæmorrhage to occur before the terminal phase, and in five of these six cases the final cardiogram was taken two or more days before death. But in the sixth case, that of Elliot and Evans (1936), a cardiogram was taken only a few hours before death and showed changes considered to be typical of a recent infarction of the posterior wall. At autopsy no infarct was found and the coronary arteries were patent. Were loss of blood an important factor in the production of the cardiographic changes, similar cardiograms might be expected to result from hæmorrhage and shock from other causes but we could find no example.

The cardiographic changes in dissecting aneurysm are not those typical of cardiac infarction. David *et al.* (1947) were of the opinion, from a study of their 14 cases, that although no cardiogram could be considered entirely normal, yet changes definitely suggestive of acute myocardial infarction were never present, even in those cases in which the coronary arteries themselves were involved in the dissection. At least two cases are on record with dissection involving both coronary arteries in which the cardiogram remained normal (Mallory, 1946; 1947). The absence of any single cardiographic appearance pathognomonic of dissecting aneurysm has also been stressed (Ritvo and Votta, 1944; Baer and Goldburgh, 1948). In many of the recorded cases the cardiograms are not reproduced. Nevertheless, from a study of the available material certain features stand out which are found in almost all cases. The commonest change would appear to be an elevation of the RS–T segment, usually accompanied by T wave inversion, affecting predominantly either standard lead I or lead III. Another feature in these cases is the absence of Q waves. This would be consistent with the rarity of actual myocardial infarction already mentioned. A similar absence of Q waves was noted by East and Oram (1948) in their patients with cardiac pain in whom ultimate recovery of the T wave occurred. Presumably in both cases the interference with the coronary circulation is of a reversible nature and is likely to be due to spasm. Yet another feature of the cardiogram in dissecting aneurysm, as illustrated by McGeachy and Paullin (1937), is its lability, striking alteration often occurring in the course of a few days. The case described by Sacks (1945) shows that these variations may not always be as haphazard as might at first appear. Here, the signs of myocardial ischæmia disappeared in the final cardiogram taken on the day of death, and the author suggests that the terminal rupture into the pericardial sac relieved the pressure on the coronary ostia resulting from dissection about the root of the aorta. Perhaps similar factors might account for the terminal diminution in intensity in the cardiographic changes seen in the case described by Bayley and Monte (1943) for here, too, rupture into the pericardial sac had occurred.

Summary and Conclusions

From a study of the reported cases it is seen that interference with the coronary blood supply in dissecting aneurysm can arise in several ways, some demonstrable at autopsy and some conjectural. It can be shown *post-mortem* to have resulted from the dissection of the aorta occluding the coronary ostia, or extending into the coronary arteries; compression of the coronary arteries from without by blood extravasated from the leaking aneurysm can also be demonstrated at autopsy, as in our case; compression within the pericardial sac by blood clot or pericardial adhesions has been suggested but we feel that this is unlikely; relative myocardial ischæmia has been considered to result from massive hæmorrhage from the aneurysm but, again, we feel that there is no strong evidence in favour of this view; incidental myocardial infarction is also a possibility. Although there are no pathognomonic cardiographic changes, we would draw attention to several characteristic features, namely the absence of abnormal Q waves, the presence of RS–T segment elevation, the transient and often rapidly changing nature of the curves, and the fact that the cardiogram is not typical of acute infarction. Actual infarction is very rare in these cases. Dissection of even both coronary arteries can occur without cardiographic change. We record an example in which both coronary arteries were surrounded by extravasated blood, the cardiogram indicating that the area of ischæmia was limited to the antero-lateral part of the left ventricle.

This problem is of practical interest because it may be most difficult clinically to differentiate cardiac infarction from dissecting aortic aneurysm. The finding of cardiographic changes suggesting involvement of the coronary arteries may add to the difficulties. Fortunately, when the cardiogram that results from involvement of the coronary arteries by a dissecting aortic aneurysm is studied, it is found that, although it differs from that typical of cardiac infarction, it has several features of its own, which should suggest the correct diagnosis.

We are indebted to Dr. Terence East for his helpful criticism of this paper, and we would like to thank also Dr. A. J. Nimmo who referred the patient to one of us (S.O.).

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THE CARDIOVASCULAR SYSTEM IN GARGOYLISM

BY

STUART LINDSAY

From the Division of Pathology, University of California Medical School, San Francisco, California

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Of interest to cardiologists is a large group of rare systemic diseases in which involvement of the cardiovascular system may produce clinical evidence of cardiovascular disease, or may lead to cardiac failure (Weiss, 1939). An attempt has been made to outline the basic clinical, laboratory and pathological features of a few of these processes (Saphir, 1942; Weiss *et al.*, 1943; Lindsay, 1946). The accompanying cardiac manifestations may then be correctly interpreted as a part of a generalized disease, and thus be differentiated from the more common forms of cardiac disease. The importance of an accurate ætiologic classification of these rare diseases has been emphasized previously (Weiss *et al.*, 1943) since factors of specific therapy must be considered.

Gargoylism, a rare disease of infancy and childhood, has been shown to belong to this group of obscure, miscellaneous systemic processes. In recent pathological studies of gargoylism, it was found that the heart and vascular apparatus are often significantly involved in this diffuse disease (Lindsay *et al.*, 1948), and furthermore that a high percentage of children with gargoylism have clinical evidence of cardiovascular disease or die from cardiac failure.

It is the main purpose of this report (1) to review the clinical manifestations of gargoylism, stressing those of cardiovascular origin, (2) to summarize the available pathological data, particularly in regard to the heart and vascular system and (3) to record an additional case of gargoylism occurring in infancy, in which involvement of the heart by the storage process was responsible for acute fatal myocardial failure.

General Characteristics

Previous pathological studies have shown that gargoylism is a generalized disease in which almost all tissues in the body are the sites of an abnormal storage process (Kressler and Aegerter, 1938; Strauss, 1948; Lindsay *et al.*, 1948). Unlike the majority of storage diseases in which the reticulo-endothelial system alone shows extensive involvement, gargoylism is characterized by the deposition and retention of a macromolecular substance mainly in parenchymal cells and in fibroblastic and other supporting connective tissues. In the earlier studies on limited autopsy material (Ashby *et al.*, 1937) it was generally agreed that gargoylism was a lipid storage process, though Kressler and Aegerter (1938) found variable histochemical staining reactions. Washington (1940) proposed the term lipochondrodystrophy. More recent pathological studies have shown that the material stored in the altered cells gives the histochemical reactions of glycogen. Furthermore there is evidence that this carbohydrate is combined with protein as a glycoprotein (Lindsay *et al.*, 1948).

There is no evidence of altered carbohydrate metabolism in gargoylism, except for the recording of abnormal galactose tolerance tests in a few instances. This indicates that the stored carbohydrate represents a complex macromolecular substance which can not be disposed of or degraded by the tissue cells and does not enter the carbohydrate turnover of the body.

Clinical evidence of the disease is not generally apparent until the stored material accumulates in quantities sufficient to alter the structure or interfere with growth of the skeletal or other tissues. While signs of the disease may be present at birth, usually these do not make their appearance until near the end of the first year of life.

Recurrence of the disease in families has been noted often, even in as many as three generations. Halperin and Curtis (1942) believe that the disease is most likely due to the action of a single recessive autosomal gene. The inheritance of glycogen disease (Von Gierke's disease) is also believed to be due to a Mendelian recessive characteristic (Abramson and Kurtz, 1946).

Over 150 cases of gargoylism have been recorded; the bibliography of the majority of these have been collected elsewhere (Lindsay and Reilly, 1948, and Strauss, 1948).

Clinical Picture of Gargoylism

These children usually have such a characteristic appearance as to suggest a familial relationship (Fig. 1). The external manifestations ordinarily appear at 1 to 1½ years of age, though one of our patients showed the typical facies at 3 months. In one recorded case, the child was described as having a repulsive appearance with a deformed skull at birth (Ashby, Stewart, and Watkins, 1937). Some children had corneal clouding at birth. The grotesque appearance of these little creatures led to the application of the term gargoyle by Ellis and his co-workers (1936).

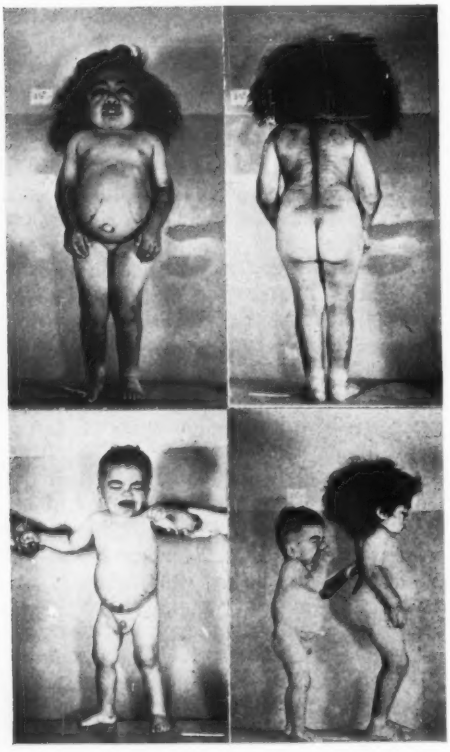

FIG. 1.—Typical gargoylism showing dwarfism, hirsutism, hepatosplenomegally, umbilical hernia, and skeletal deformity. The boy is 3 years of age and the girl 13 years of age.

There is relative enlargement of the head. The facial features are coarsened and the nasal bridge is depressed. The eyebrows are thick. The eyes appear protruding. The mouth is usually open and almost filled with an enlarged protruding tongue. The external ears appear enlarged and the aural cartilage is often soft and unusually flexible.

The alterations of the skeleton are particularly striking. The stature is short, mainly due to shortening of the legs. The neck is usually shortened and thickened. There is often an increase in the anterior-posterior diameter of the chest, at times with unusual prominence of the sternum and posterior bowing of the costal cartilages. Dorsal kyphosis near the thoracolumbar junction was present in 12 of one group of 14 patients. These patients stand with a partial crouch, with the thighs and knees partially flexed. There is similar flexion of the elbows and the hands are usually in ulnar deviation. The small joints of the wide stubby hands and feet are held in a flexed position giving a clawed appearance.

Shortening of the mandibular rami with increased obtuseness of their angles is often associated with widely spaced, peg-shaped teeth.

The abdomen is protuberant. The liver and spleen are enlarged, and are usually palpable by the end of the first year; they are smooth and firm. An umbilical hernia is almost invariably present, and inguinal hernias have been present in a number of male patients.

Most children with gargoylism develop cloudiness of the corneas, and progressively diminishing vision. This clouding is due to the presence of punctate refractile deposits (slit lamp) mainly in the deeper corneal fibres. Reduction in ability to hear or even total deafness usually appears by the 6th to 12th month.

Hirsutism of the trunk and extremities, as well as of the scalp, neck, and eyebrows has been present in over half the patients.

One of the most prominent findings, often antedating the skeletal and other external manifestations, is chronic nasal infection with profuse nasal discharge and severe nasal obstruction. This is probably responsible for the frequency of pulmonary infections so often noted in these children.

Most of these children show progressive mental deficiency beginning at about 6 to 18 months after the onset of the other clinical manifestations of the disease. Three of 15 patients whose intelligence was tested had normal mentality. One of the three died at the age of 11 years, and pathologic examination of the brain showed storage involving only some of the connective tissue cells of the central nervous system (Reilly and Lindsay, 1948). The brains of those with retarded mental growth have shown extensive storage of the macromolecular substance in the cytoplasm of almost all portions of the central and peripheral nervous system, involvement sufficient to account for the usual clinical evidence of mental disease (Lindsay *et al.*, 1948).

Laboratory Findings in Gargoylism

Examination of the blood in our series of patients (Reilly and Lindsay, 1948; Lindsay *et al.*, 1948) has shown mild hypochromic anæmia in 10 of 16 patients. Six had white blood counts of 5000 per cu. mm. or below. At times, some of these patients have shown a relative lymphocytosis. In eight patients, abnormal dark-violet granules (Wright's stain) have been demonstrated in the white blood cells (Reilly, 1941). These are found mainly in the neutrophilic leucocytes. The number of involved cells fluctuates widely. More recent studies (Lindsay *et al.*, 1948) have suggested that these granules may consist of the same carbohydrate material widely stored in other tissue cells.

Urinalysis gave normal findings in all the cases. Reducing substances have never been demonstrated in the urine. In five children, blood lipid analyses were done. One showed lipæmia and hypercholesteræmia. A variety of other chemical examinations of the blood showed nothing abnormal as a rule. In one child a hippuric acid test gave abnormal results. In another, there was prolonged retention of galactose in the blood after intravenous injection. With that exception, carbohydrate tolerance tests gave normal findings.

Serological tests for syphilis were done in 14 of the patients; all gave negative results.

Roentgenographic Findings

In well developed cases, the skeletal alterations of gargoylism are characteristic and have been described in detail elsewhere (Reilly and Lindsay, 1948). Changes in the skull include enlargement and shallowness of the sella tursica and prominence of the frontal bones. The scapulas are widened, and the ribs are broadened and distorted. Notch-like irregularities of the lower thoracic and lumbar vertebral bodies often produced dorsal kyphosis. Pronounced lesions are demonstrated in the extremities, where the shaft of the long bones tends to be short and broad with bizarre central swellings. There is delay of epiphyseal maturation and the epiphyseal plates are usually flat and deformed. Those of the radius, ulna, and tibia are often angulated. Irregular widening of the phalanges, metacarpals, and metatarsals account for the claw-like hands and feet of these children. Two patients had encephalograms; one showed frontal cerebral atrophy, and the other internal hydrocephalus.

Histological Lesions in Gargoylism

The characteristic cellular lesion in gargoylism is enlargement due to swelling of the cytoplasm. The latter may be almost entirely clear and colourless and surrounded by a thin cellular membrane. In some cells, the central perinuclear portion of the cell is occupied by a clear vacuolated space, surrounded by condensed peripheral cytoplasm. In still other cells, the cytoplasm may have a coarse or fine granularity which represents a fragmented residual cytoplasmic network surrounding tiny vacuolated spaces. Some nerve cells show this alteration only in one portion of their cytoplasm.

A variety of cell types are included in the storage process. Epithelial cells, particularly of the liver, are markedly altered. The epithelium of the skin and its glands, and the anterior lobe of the pituitary gland are among the other epithelial tissues involved. Nerve cells of all portions of the central and peripheral nervous system are sites of deposition. Reticuloendothelial cells, both fixed and wandering, show the same vacuolization of the cytoplasm, particularly in the spleen and lymph nodes. The most striking tissue changes are observed in the mesodermal connective tissues. Fibrocytes, chondrocytes, and osteocytes all show enlargement and vacuolization of their cytoplasm. Since the intercellular substances supporting these cellular elements are derived from their cytoplasm, and since the cellular cytoplasm is altered due to the storage process, it is not surprising that the intercellular connective tissue substances have an abnormal appearance. In some situations, particularly in the cardiovascular system, the storage process in fibroblastic cells was associated with increased amounts of altered collagenous intercellular substances. Most collagenous fibres had lost their normal fibrillary characteristics, and appeared swollen and homogeneous. Osteomucin and chondromucin frequently had a fibrillary or mucoid appearance and were poorly formed. These alterations of connective tissues, associated with lack of normal osteoblastic activity, particularly at epiphyseal lines, appears to be a prominent factor in the retarded skeletal growth in these children.

Cardiovascular Symptoms and Signs

In the published reviews of gargoylism, cardiovascular signs and symptoms, occasionally with death from cardiac failure, are frequent (Reilly and Lindsay, 1948, and Strauss, 1948). While Ellis and his co-workers (1936) mentioned no cardiovascular abnormalities in the 15 patients reviewed by them, Washington (1940) recorded three cases of gargoylism with death resulting from cardiac failure.

The clinical records of 16 cases of gargoylism previously reported (Reilly and Lindsay, 1948) were reviewed for evidence of cardiovascular disease: 2 presented symptoms that may have been of cardiovascular origin, 11 had physical or roentgen signs of cardiovascular disease at some time during the course of their illness, and of the 8 fatal cases with autopsies, 4 died of cardiac failure.

Of an additional 16 reported fatal cases, 3 were reported as presenting symptoms of cardiac disease, and 5 had clinical signs of cardiac abnormality. In several reports, the cardiac status was not mentioned. Nine of the 16 additional reported patients who succumbed to their disease appear to have died of cardiac failure. The recorded cardiovascular signs and symptoms and cause of death in all these cases have been summarized in Table I.

Pathological Cardiovascular Lesions in Gargoylism

Gross Lesions. Of the 25 patients with gargoylism on whom an autopsy was done, the weight of the heart was recorded in 16; in 13 of these, there was cardiac hypertrophy. The weight of the heart varied from 10 to 147 grams more than the average normal weight for the patient's age. In two instances, the weight of the heart was increased two and three times respectively. In two cases, the cardiac weight was within normal limits, and in one the weight was slightly less than normal. Considering that dwarfism is usual, the degree of cardiac hypertrophy is generally extreme.

In 4 of the 25 patients, there was opaque thickening of the epicardium, in one instance involving

TABLE I

CARDIOVASCULAR FINDINGS IN GARGOYLISM

Author	Age (years) and sex	Symptoms	Signs	Cause of death
Tuthill	M–7	None	None	Not known
Ashby, Stewart, and Watkins	M–19	None	Pulse rate 108/min. B.P. 136/50	Sudden collapse and death
,,	F–9	None	None	Congenital heart disease
Kressler and Aegerter	M–8	Paroxysmal attacks of dyspnœa	Chest film showed diffuse cardiac enlargement. Cyanosis and œdema	Cardiac failure
Berliner	M–6	Not stated	Not stated	Not stated
Hora	?–NB	Not stated	Not stated	Not stated
Stoeckel	F–4	None	None	Bronchitis
Kny	F–6	None	None	Not stated
Schmidt	?–4	Not stated	Not stated	Not stated
Rochat	F–6	Not stated	Not stated	Not stated
DeLange	F–6	None	None	Sudden unexpected death
Wolff	M–28	None	None	Cardiac failure
DeLange	M–19	Dyspnœa. Tracheal and laryngeal stridor	Præcordial systolic murmur with accentuation of 2nd sound	Suddenly during bronchoscopy
Nja	M–11	None	Cyanosis of extremities	Death with cyanosis and dyspnœa
Straus *et al.*	M–29	Exertional dyspnœa	Cyanosis, clubbing of fingers and anasarca	Congestive failure, and bronchopneumonia
Strauss	F–3	None	Pulse rate 120/min. B.P. 120/80	Sudden cardiac failure
Reilly and Lindsay	F–17 mos.	None	None	Alive
,,	M–3½	None	Soft systolic murmur at base	Alive
,,	F–8 mos.	None	At 8 months, accentuated 2nd sound and systolic murmur heard best at 3rd left interspace. At 4 years, slight sinus arrhythmia, P–R 0·12 sec., high T I and T II. At 5 years, soft systolic murmur over entire præcordium, heard best in 4th left interspace. At 11 years, sinus tachycardia (120), P-R 0·12 sec., QRS 0·07 sec.	Alive
,,	F–3	None	None	Alive
,,	F–17 mos.	None	Cyanosis at birth and for 2 days.	Alive
,,	M–4	None	None	Alive
,,	M–13 mos.	Dyspnœa and restlessness since birth	At 13 months, rapid regular pulse, harsh systolic murmur at aortic area and 3rd and 4th right interspaces. Chest film showed broad widened cardiac shadow. At 3 years, grade ii apical systolic murmur heard.	Alive
,,	F–9	None	At 19 months, tic-tac heart sounds and systolic murmur at apex. At 3 years, rough systolic murmur heard over entire præcordium. Loud diastolic murmur in the left 3rd interspace near the sternum. P2 loud and snapping. B.P. 130/90. Chest film showed widening of proximal aorta and pulmonary arterial dilation. At 7 years, signs of cardiac failure with peripheral œdema.	Cardiac failure. Autopsy not done

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TABLE I—CARDIOVASCULAR FINDINGS IN GARGOYLISM—*continued*

Author	Age (years) and sex	Symptoms	Signs	Cause of death
Lindsay, Reilly, Gotham and Skahen	M–10	Dyspnœa	Transient systolic murmur heard best at pulmonary area. B.P. 88/58	Sudden death with episode of pulmonary œdema and cardiac failure
	F–7½	None	Loud systolic murmurs at apex and pulmonary areas. Soft to and fro murmur at aortic area	Death with fever, rapid pulse and respiration, cyanosis and Cheyne-Stokes breathing
,,	M–6½	None	Peripheral arteries of arms thickened. B.P. (arms) 132/100, (legs) 180/110	Pulmonary tuberculosis
,,	M–5	None	Extrasystoles. B.P.: right arm 124/60, left arm 168/60, right leg 128/70, left leg 132/72	Broncho-pneumonia
,,	M–4	None	None	Cardiac failure with ascites
,,	M–1	None	Œdema of face, scrotum, and legs during first few weeks of life. Apical systolic murmur	Death with pulmonary congestion, dyspnœa and broncho-pneumonia
,,	M–7	None	Slight cardiac enlargement to percussion. Distant heart sounds of poor quality	Broncho-pneumonia, empyema and subdural abscesses
,,	F–3	None	None	Broncho-pneumonia
Present case	M–4½ mos.	Dyspnœa	None	Sudden death with dyspnœa and cervical rigidity

both left and right ventricular surfaces. In three instances, there was similar diffuse thickening of the endocardium, mainly of the ventricles and especially prominent near the mitral valve.

Significant left ventricular hypertrophy was described in seven of the autopsied cases. In one there was hypertrophy of the right ventricular wall as well. The myocardium was pale and firm in one, and in the case described in this paper was soft and greyish red. The presence of myocardial fat was mentioned in one case.

The valvular lesions are probably the most striking cardiac abnormalities seen in this disease, and were described in 14 of the 25 recorded fatal cases. In one, the mitral and tricuspid valves were described as " congested " (Ashby, Stewart, and Watkins, 1937), and in one the valvular lesion was described only as " chronic endocarditis " (Stoeckel, 1941). More adequate descriptions are available in the remaining 12 cases.

In the one reported by Kressler and Aegerter (1938) the mitral valve was thickened, scalloped, and showed orange pigmentation of the cusps; the edge of the posterior mitral leaflet and the base of the aortic valve were calcified. Wolff's case (1942) showed chronic endocarditis of the aortic, mitral and tricuspid valves with aneurysmal dilatation of the margins of the mitral and tricuspid valves. In one of DeLange's patients (1944), the mitral cusps were diffusely thickened and stiffened, but had smooth surfaces; there was shortening and fibrous thickening of the mitral chordæ tendineæ. The tricuspid valvular cusps were thickened, but still flexible. The pulmonic valve was normal, but the free edge of the aortic valvular cusps was thickened. Nja's case (1945) had thickening of both the aortic and mitral valves; in the latter, the thickening was nodular and the attached chordæ tendineæ were shortened and thickened. In the case recently reported by Strauss (1948), there were numerous 3 mm. nodules with smooth surfaces, distributed along the mitral and tricuspid

valves at the insertions of the chordæ tendineæ, which were short and thick; these nodules had a fibrous consistency. The aortic and pulmonic valves were œdematous and fleshy.

In the material examined at the University of California Hospital, seven of nine patients (including the one presented in this paper) had valvular lesions. In all instances, the mitral valve showed the characteristic lesion (Fig. 2). In two, the tricuspid valve was similarly involved, and in one the aortic and mitral valves were both altered. In another case in this series, all the valves were affected by the pathological process.

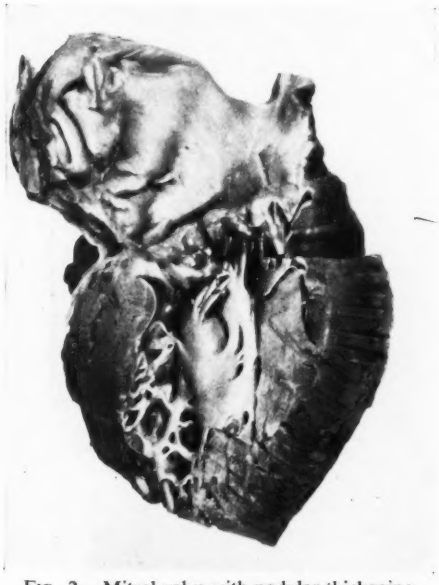

FIG. 2.—Mitral valve with nodular thickening and shortening of chordæ tendineæ.

Alteration of the mitral and tricuspid valves is characterized generally by a nodular fibrous thickening along the free edge and line of closure of the valve. These nodules are usually coalescing and have a glistening translucent appearance. They vary between 1 mm. and 3 mm. in diameter. The diameter of the chordæ tendineæ of these altered valves is several times the normal diameter; these structures are contracted and shortened, and have an opaque fibrous appearance. Mitral stenosis was the result of this process in one case.

When involved, the aortic and pulmonary cusps show a rolled free edge. While the thickening has the moist fibrous appearance of the mitral valvular lesion, the margin of the valve is not usually nodular, and may be slightly retracted.

Of the reported fatal cases of gargoylism, three have shown gross evidence of coronary insufficiency. Thus in Strauss's case (1948), the coronary arteries were widely patent, but had stenotic, slit-like orifices. In two (Lindsay *et al.*, 1948), pronounced coronary arterial thickening could be seen. In one of these, the coronary arterial system appeared prominently on the epicardial surface as rigid white cords. In both instances, the intimæ was greatly thickened and consisted of a layer of grey, glistening translucent fibrous tissue; this left small pin-point or slit-like lumens. The altered intima contrasted sharply with the more compact, opaque medial layer.

Of the 25 recorded autopsies, macroscopic aortic lesions were described in 7 instances. Kressler and Aegerter (1938) found orange intimal streaking of the ascending aorta. In the case of DeLange *et al.* (1944) there was linear lipid infiltration of the posterior aortic wall. Strauss (1948) described thickening of the aorta and its major branches; the aortic intima was white, wrinkled, and contained yellow plaques.

In the group of eight patients previously reported, gross aortic lesions were described in three (Lindsay *et al.*, 1948). In the aorta of one ten-year-old boy, there were three small intimal plaques just distal to the valve. In the case of a four-year-old boy, there were four oval elevated yellow plaques just distal to the valve. In the third case, numerous small yellow plaques were found just distal to the valve, and there were small linear yellow streaks in the thoracic aorta, most numerous about the intercostal arterial ostea. In addition, there were a few longitudinal streak-like plaques which were grey in colour in this segment of the aorta.

Gross alteration of other vessels had been described in only two cases. In one (Strauss, 1948) there was slight thickening of the pulmonary arterial branches. In another, one of the main pancreatic arteries showed translucent intimal fibrous thickening (Lindsay *et al.*, 1948).

Visible renal alteration has been described in a few instances. Where the renal weights have

been recorded, these have been close to the normal average weight for the age with one exception. In relation to body size, the kidneys were often enlarged. Generally the gross appearance has not been significantly altered. In two cases the cortical layers showed yellowish-pink pallor.

Microscopic Lesions. Microscopic pathological lesions in the cardiovascular system of a fairly uniform and characteristic type have been described in 12 patients. Connective tissues of the pericardium, myocardium, endocardium, valves, and coronary vessels have shown a similar alteration. The fibroblastic cells were swollen and enlarged. Their cytoplasm was clear, vacuolated, or granular. There was an increase in the amount of intercellular collagenous stroma, and this material usually had undergone hyaline or mucoid changes. The normal fibrillary characteristics were lost, and the fibres often appeared œdematous. The cellular swelling, and the alteration of the intercellular collagen often produced a pseudocartilagenous appearance in the involved cardiac connective tissue.

The fibrous thickening and cellular alteration in the valves and endocardium was greater than elsewhere in the heart, and accounted for the nodular deformity of the valves and the widening and thickening of the chordæ tendineæ. In a few instances minimal chronic inflammatory cellular infiltration and either large or small calcific deposits have been present in the altered valvular connective tissue. In two cases, lipid droplets have been demonstrated in some of valvular fibroblasts, but the amount of this material did not account for the degree of cellular enlargement. DeLange *et al.* (1944) were unable to demonstrate the presence of glycogen in the altered cells.

Myocardial alteration has been described in several instances. Kressler and Aegerter (1938) described vacuolization of the myocardial nuclei and fibres. There was atrophy and fraying of some cardiac muscle fibres associated with an increase in myocardial connective tissue in one of DeLange's cases (1944). Strauss (1948) found atrophy of myocardial fibres with replacement by large vacuolated cells; other fibres were hypertrophied. Three of our cases (Lindsay *et al.*, 1948) showed vacuolization of the myocardial fibres; in one instance the vacuoles contained bluish granular material.

The coronary arterial system shares in the connective tissue alteration in gargoylism. Strauss (1948) found segmental medial thickening of the medium size coronary arterial branches; the media contained large vacuolated cells. Four of the cases from this clinic have shown intimal fibrous thickening of the main coronary arteries and the major branches. In three cases this process greatly narrowed the arterial lumens, and two of these died of cardiac failure. The thickened intimal layer consisted of moderately dense wavy collagenous fibres with a concentric arrangement. The fibres were usually swollen, and appeared less fibrillary than normal. Lying between the fibres were elongated clefts containing large swollen fibroblasts with clear cytoplasm. There was pressure atrophy of the surrounding media, and the adventitial connective tissue usually showed changes similar to those of the other cardiac connective tissues.

The storage reaction involves the aortic wall as well as the heart in this disease. There was intimal thickening and swelling of the medial connective tissue cells in the cases described by DeLange (1944) and Strauss (1948). In five of our cases aortic microscopic lesions have been demonstrated. The intima was thickened and composed of hyalinized collagenous connective tissue containing distorted vacuolated fibroblastic cells. In a few instances, the superficial part of the intima contained groups of foamy macrophages in which lipid material could be demonstrated. The elastic tissue fibres of the media were usually very distinct and were separated by fusiform clefts containing altered swollen connective tissue cells (Fig. 3). Some of these cells contained pale greyish blue granular material. The adventitial connective tissue usually had a similar appearance.

In several of the recorded cases, similar though less severe intimal thickening has been described in carotid, mesenteric, pancreatic (Fig. 4) and renal arteries. The medial muscular cells have been vacuolated as well.

While renal lesions have not been described in cases elsewhere, five of the nine fatal cases examined in this laboratory have shown distinctive glomerular alteration of varying degrees

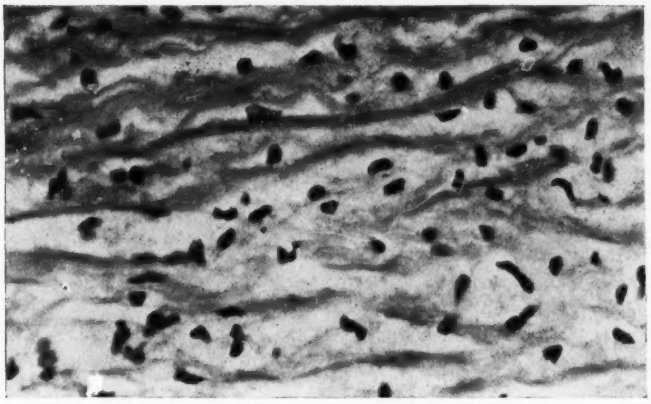

FIG. 3.—Aortic media showing swelling of connective tissue cells. Magnification × 500. Hæmatoxylin and eosin stain.

of severity. These lesions bear resemblances to those of glomerulonephritis. While the frequent chronic recurrent respiratory infection in these patients might well result in glomerulonephritis, the lesion has certain characteristics resembling the other altered tissues in this disease. There are increased numbers of both epithelial and endothelial cells in the glomeruli resulting in glomerular enlargement and narrowing of the capillary channels (Fig. 5). The glomerular tufts are occasionally adherent to each other, and to the glomerular capsules. Some glomeruli have shown epithelial proliferation in the capsules with formation of epithelial crescents. The basement membranes were usually swollen and frayed, and some had deposits of amorphous grey granular

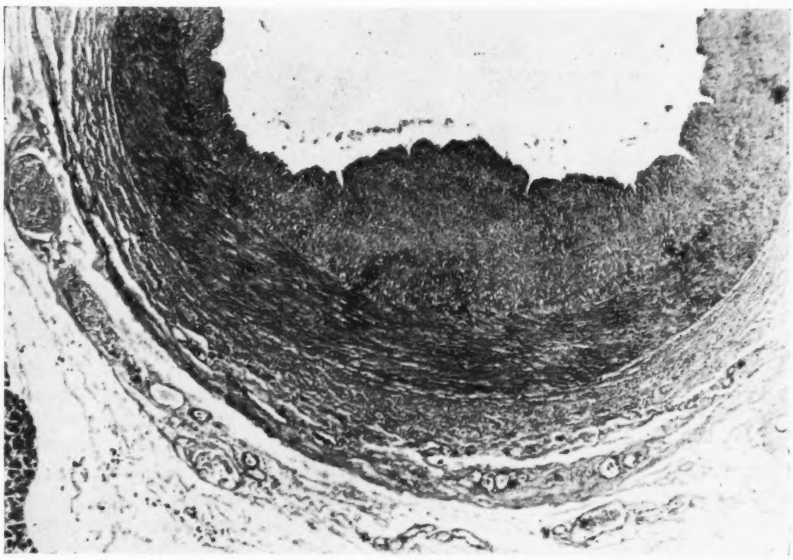

FIG. 4.—Pancreatic artery showing intimal thickening. Magnification × 45. Hæmatoxylin and eosin stain.

material. There were often desquamated cells and precipitated protein in the glomerular spaces. Abnormal vacuolization of the convoluted tubular epithelial cells frequently accompanied the glomerular lesions. It is of interest to note that one of these children with pronounced glomerular lesions had a phenolsulphonephthalein excretion test of 23 per cent.

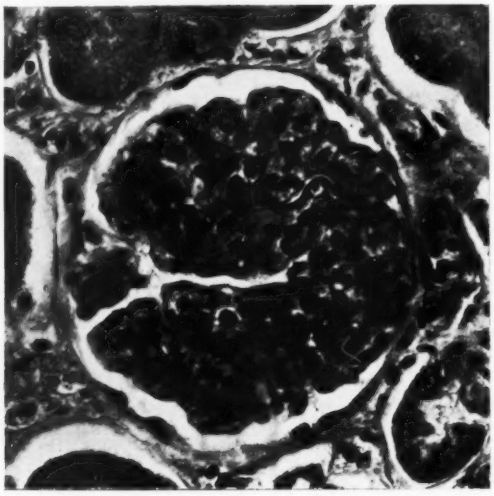

FIG. 5.—Glomerulus showing increased cellularity, decreased vascularity and thickening of basement membrane. Magnification × 500. Hæmatoxylin and eosin stain.

EXTRACARDIAC FACTORS CONTRIBUTING TO CARDIAC EMBARRASSMENT

There are several extracardiac factors operating that should be noted as probably contributing to cardiac embarrassment. One is the thoracic deformity, which includes narrowing of the transverse diameter of the chest with anterior prominence of the sternum, posterior bowing of the costal cartilages and an increase in the dorsal curvature of the thoracic spine. Elevation of the diaphragm by the enlarged liver and spleen appears to diminish further the volume of the thoracic cavity.

Chronic interstitial pneumonitis, usually with histologic evidence of the abnormal storage reaction in the pulmonary tissues is a common lesion in gargoyles. It is probably secondary to the common chronic nasopharyngeal inflammation which in turn is secondary to the bony deformities of the nose and nasal passages.

Anæmia, at times of severe grade, is a third factor that may be responsible in part for the cardiovascular signs and symptoms in this disease.

DIAGNOSIS

While the fully developed syndrome of gargoylism should present no diagnostic difficulties, some cases have not shown the complete clinical picture. Thus mental retardation or corneal clouding has been absent in some of the recorded cases that otherwise had the typical facies, hepatosplenomegaly, dwarfism, and skeletal deformities. These changes do not occur together in any other disease. The external appearance of these children resembles that of cretinism; both at this clinic and elsewhere, substitution thyroid therapy has shown little if any effect on growth. While the serological reactions have been consistently negative, some patients have been given antiluetic therapy because of the resemblance of the cloudy corneas to those of congenital syphilis. Such therapy has been without benefit. A diagnosis of hypertelorism has been suggested in some instances

because of the increased intra-orbital distance. Because of the frequency of demonstrable systolic murmurs along the left sternal border, 4 of 16 patients with gargoylism reported from the University of California Medical School were suspected of having a congenital interventricular septal defect. Pulmonary stenosis was suspected in one. Rheumatic heart disease was not considered in the differential diagnosis in this group of cases.

Similarities of Pathological Cardiovascular Lesions to those of Glycogenosis

The pathologic lesions in the heart and other tissues in gargoylism have some resemblance to those of glycogen disease (Von Gierke's disease). Both these conditions differ from the other storage processes in that the glycoprotein or glycogen is deposited mainly in parenchymal or fibroblastic cells rather than in reticulo-endothelial cells.

Since Von Gierke's pathological description of glycogen storage disease in 1929, it has become apparent that there were two principal forms of the disease: (1) the type characterized by excessive storage of glycogen in the liver and (2) glycogen storage disease involving the heart; the latter appears to include true excessive glycogen storage in the cardiac muscle fibres and congenital cardiac rhabdomyoma. The differentiation of these lesions has recently been reported. Haymond and Giordano (1946) have reviewed the subject of glycogen disease of the heart, and stressed the characteristic vacuolization of the cardiac muscle fibres. Mason and Anderson (1941) collected 11 cases demonstrating that these vacuoles represented glycogen deposits, and ten of their cases were infants who died from myocardial failure and pneumonia between 5 and 8 weeks of life. Sudden death has been reported (Van Creveld, 1939). While the cardiac enlargement may be enormous, generally there is no alteration of the pericardium, endocardium, valves, or coronary blood vessels. However, glycogen accumulation in the walls of arteries and veins has been described (Hueper, 1942). The myocardium has been described as pale brownish or reddish-pink or having greyish streaks. In the nodular form of glycogen storage disease of the heart, Haymond and Giordano (1946) showed additional histological changes similar to those occurring in gargoylism. In the involved areas, the small coronary arterial twigs showed mild perivascular fibrosis and fibrous intimal thickening. Loose areolar connective tissue with oval vesicular nucleii had replaced many of the myocardial fibres. This connective tissue somewhat resembled the subendocardial and intimal coronary arterial fibrosis of gargoylism.

Case Report

G.G., a 4½-months-old male child, was well until 18 hours before death. On examination the child was found to have respiratory difficulty and stiffness of the neck. Since there was no improvement in the infant's condition by the following morning, admission to hospital was advised. En route to the hospital, the infant became unconscious and expired.

Autopsy Report. The autopsy was performed at the San Francisco Coroner's Office seven hours after death by Drs. Jeanne I. Miller and Henry D. Moon. The infant was large, and appeared well developed and nourished. External manifestations suggestive of gargoylism were not noted. The fontanelles were slightly depressed.

The peritoneal cavity contained approximately 50 ml. of clear serous fluid. The pleural cavities contained small amounts of sanguinous fluid; the pericardial cavity was normal.

The heart was enlarged and weighed 90 g. after fixation in 10 per cent solution of fomaldehyde U.S.P. The diameter of the heart was greater than half the transverse diameter of the thoracic cavity. All the cardiac chamber were dilated and in addition there was hypertrophy of the wall of the left ventricle. The epicardium was slightly opaque and granular, and there was scanty epicardial fat. The myocardium of both the left and right ventricles was soft and had a mottled, greyish-red colour. There was diffuse, opaque thickening of the endocardium of the left and right ventricles. The valves and chordæ tendineæ showed nothing abnormal. The ductus arteriosus was barely

patent; the foramen ovale was closed. The coronary arteries had a normal appearance. The thoracic aorta showed no coarctation.

The thymus gland weighed 35 g., and measured $5 \times 5 \times 2{\cdot}5$ cm. It appeared normal externally and on section.

The right lung weighed 120 g., and the left lung weighed 60 g. Both lungs had smooth but deeply congested pleural surfaces. The pulmonary parenchyma showed considerable congestion and intra-alveolar fluid. While the tissue was more firm than normal, there was no consolidation.

The liver was of normal size and weight. The anterior edge of the right lobe was sharp. The parenchyma was pale, and pinkish-tan in colour. The spleen weighed 30 g. The capsule and pulp were normal The gall bladder and pancreas showed nothing abnormal. The entire gastroenteric tract was normal, though the mesenteric lymph nodes appeared moderately enlarged. The adrenal glands were normal. Each kidney weighed 30 g. The surfaces were smooth, and the cut surfaces showed normal markings and colour. The calyces, pelves, ureters, bladder, and genital system were normal.

The aorta and bone marrow showed no gross pathological lesions.

The scalp, skull, and dura were normal. The brain weighed 860 g. The meninges appeared normal. The superficial markings and blood vessels appeared normal. Serial coronal sections through the cerebral hemispheres, cerebellum and brain stem showed no lesions.

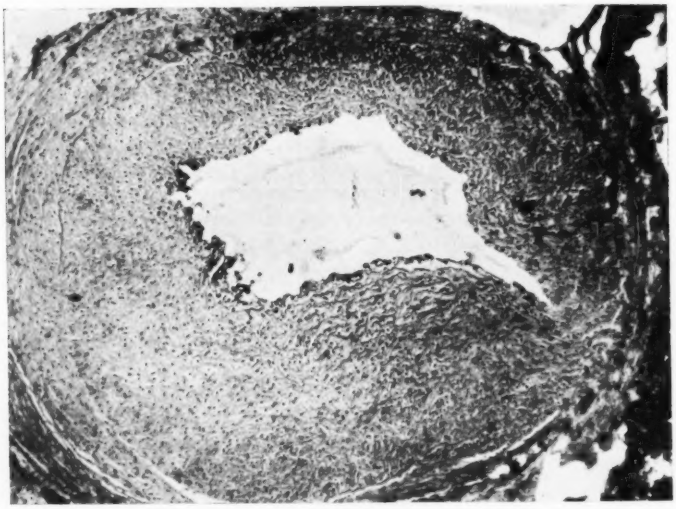

FIG. 6.—Large coronary artery with intimal fibrosis. Magnification $\times 80$. Hæmatoxylin and eosin stain.

Microscopical Examination. Blocks of tissue fixed in 10 per cent solution of formaldehyde U.S.P. and embedded in paraffin were kindly made available for study by Dr. Henry D. Moon.

The main coronary arteries all showed narrowing of their lumens due to marked intimal thickening (Fig. 6). The intimas were composed of concentrically arranged, wavy, collagenous fibres which surrounded fibroblastic cells. The latter had either completely clear or vacuolated cytoplasm. The media of these coronary arteries was narrowed but the adventitial layer was normal.

The opaque thickened ventricular endocardium had a similar histological appearance (Fig. 7). The abundant collagenous fibres were swollen, frayed, and vacuolated. Often they had lost their fibrillary appearance. They enclosed fusiform fibroblastic nuclei which had abundant swollen, clear or vacuolated cytoplasm. The connective tissue of the bases of the mitral and aortic valve was

similarly altered (Fig. 8). The pericardial layer was not abnormal. Some myocardial fibres were fragmented, and a few had disappeared. There was no vacuolization of their cytoplasm. There was similar alteration of the connective tissue cells of the adventitia of the smaller coronary arteries in the myocardium.

The intima of the proximal portion of the aorta was thickened and fibrotic. It consisted of an irregular network of hyaline collagenous fibres surrounding enlarged vesicular fibroblastic cells. The media had a similar appearance with almost total disorganization of the normal elastic tissue

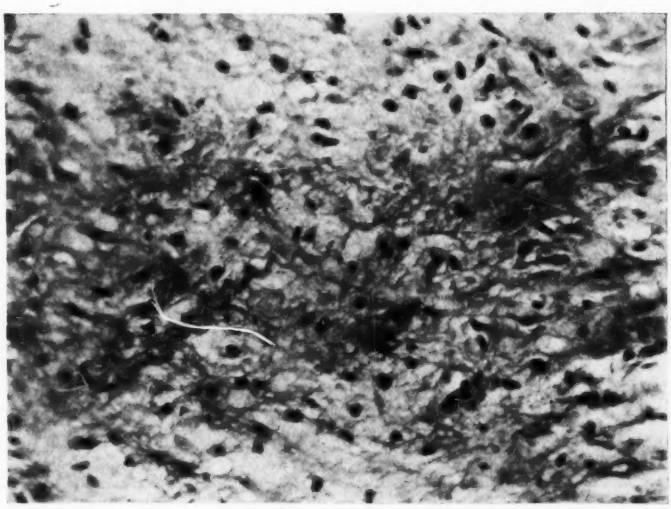

FIG. 7.—Endocardium showing fibrous thickening and cellular swelling. Magnification ×320. Schiff's stain.

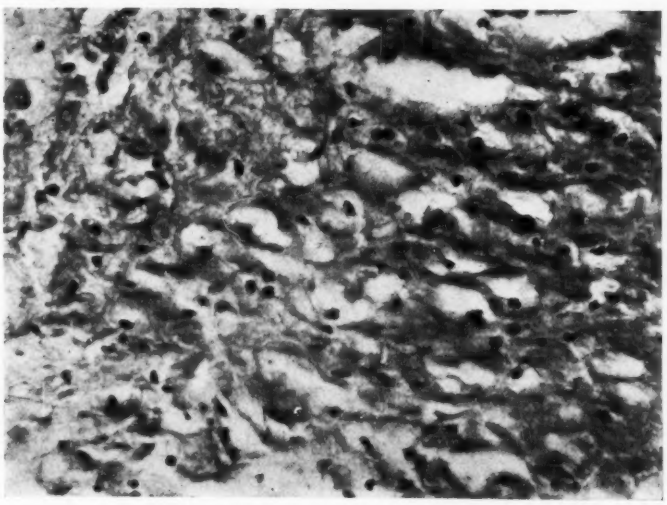

FIG. 8.—Base of aortic valve showing cellular swelling in connective tissue. Magnification ×320. Schiff's stain.

pattern (Fig. 9). A large adventitial artery had a markedly thickened intima with similar histologic changes as already described. The media was atrophic and the lumen was narrowed (Fig. 10). Small interstitial hæmorrhages were present in the epicardial and myocardial layers. A few dark pink granules were seen in a few myocardial fibres with the Schiff stain (McManus, 1946).

There was marked vascular congestion of the lungs. There was abundant serous fluid in the alveolar spaces and interlobular septa. The latter also contained numerous large macrophages with vacuolated cytoplasm. There was no inflammatory reaction.

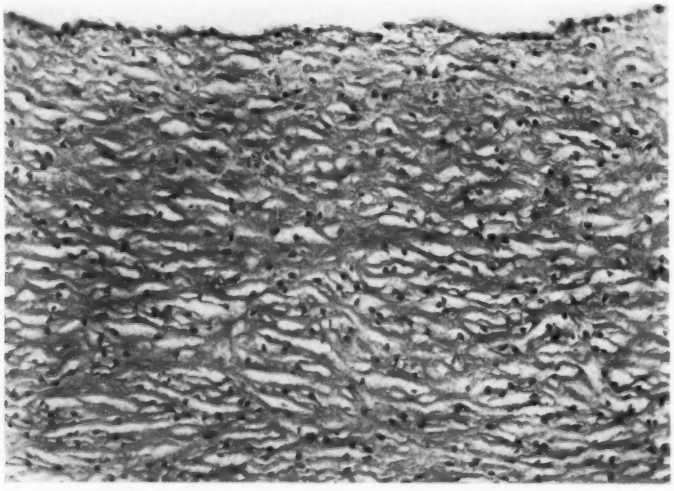

FIG. 9.—Aorta showing large clear connective tissue cells . Magnification ×80. Schiff's stain.

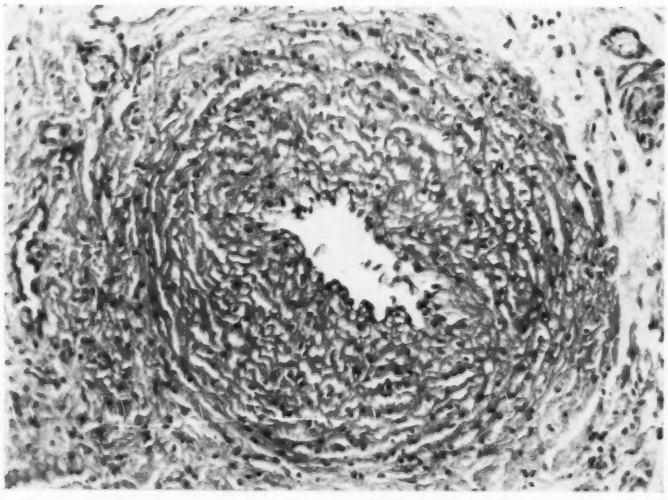

FIG. 10.—Small artery in aortic adventitia showing intimal thickening. Magnification ×80. Schiff's stain.

The hepatic cells were enlarged and had distinct cellular membranes (Fig. 11). The thin outer layer of cytoplasm was condensed and eosinophilic, while the inner portion was finely granular and vacuolated. The portal and central spaces were not altered, and there was no cirrhosis. The Schiff stain showed a few dark pink granules in a few of the Kupffer cells.

The splenic lymphoid follicles were large, poorly defined and had small germinal centres. In the splenic pulp many of the reticulo-endothelial cells were enlarged and had vacuolated cytoplasm. Portions of the basement membranes of the glomeruli were mildly thickened and frayed; cellularity was not increased. There was no alteration of the renal tubules, or of vascular or interstitial tissues. The gastroenteric tract showed nothing abnormal; the lymphoid tissue of the small intestine had a normal histologic appearance.

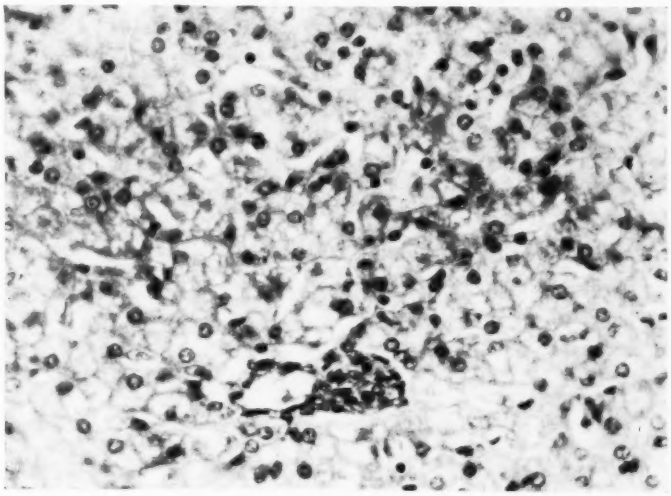

FIG. 11.—Liver showing vacuolization of hepatic cells. Magnification ×30. Schiff's stain.

The adrenal cortical cells were normal. The medullary cells were enlarged. The nuclei were normal, but the cytoplasm was swollen, finely granular and vacuolated.

The thymic lobules were large and the cortex contained numerous lymphocytes. In the medulla were many large reticular cells with abundant foamy cytoplasm.

The sinusoids of several lymph nodes were lined by abnormal reticulo-endothelial cells. These were enlarged and had abundant vacuolated cytoplasm.

Numerous sections from all portions of the central nervous system showed no abnormalities. There were no changes in the nerve cells suggesting an abnormal storage process.

SUMMARY AND CONCLUSIONS

In a review of 25 recorded autopsies in gargoylism there were 17 patients with gross or microscopic evidence of cardiovascular disease.

The average age of gargoyles dying of cardiac failure is approximately 11 years, with a range from 1 to 29 years. These fatal cases have shown the external manifestations of the disease, while the case reported in this paper appeared to present no characteristic external abnormalities. This case also differed from the others recorded in that the degree of cardiac and vascular involvement was greater than that of the other tissues. Although the liver, spleen, lymph-nodes, thymus, and adrenal gland all showed cytologic changes previously described in gargoylism, these organs

were not enlarged or otherwise grossly altered. This case not only appears to be the youngest patient with gargoylism dying of cardiac failure, but also again demonstrates that the syndrome of gargoylism may have atypical or intermediate forms. The recording of otherwise typical cases, that however lacked corneal clouding or subnormal mentality, has already suggested the existence of such incomplete forms of the disease (Strauss, 1948).

The pathological lesions of the heart and vascular system are identical with those of other connective tissues, and consist of swelling and vacuolization of the cytoplasm of the connective tissue cells. The collagenous fibres in the affected tissues are swollen and often amorphous.

While all cardiac connective tissues are generally involved in the disease process, the most pronounced lesions are in the valves and coronary arteries. It is the alteration of these tissues that appears largely responsible for failure of the heart in many instances.

Of the fatal cases of gargoylism that have been reported, including the present one, the cause of death has been recorded in 19 cases; 14 of these appear to have died of cardiac failure.

Gargoylism should be considered in the diagnosis of cardiovascular disease in infants and children.

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PURE AORTIC STENOSIS

BY

G. A. KILOH

From the Institute of Cardiology, National Heart Hospital

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This paper is concerned with cases of pure aortic stenosis occurring in subjects under the age of 50 years. Many papers have been written since Monckeberg contributed the first systematic investigation of aortic stenosis in 1904. It has been studied from many aspects, but most authors have been concerned with aortic stenosis of any degree, accompanied or not by incompetence, and irrespective of the age of the patient. Exception to this general rule has been provided by Gallavardin (1909, 1921, 1936) who contributed three papers on the subject of pure aortic stenosis, though many of his cases were not pure in the strictest sense, as there was accompanying incompetence, but only of such a degree that it could not be suspected by examination of the peripheral circulation or blood pressure. Gallavardin's conclusions have received little consideration from the British and American schools. It is widely held that pure aortic stenosis is rare and it is one of the objects of this paper to show that this idea is exaggerated. The fact that stenosis of the aortic valve can be pure should not be unacceptable when pulmonary stenosis is generally so. Pure aortic stenosis, particularly when it occurs in young people, is uncommon (though not rare) and easily overlooked.

Clinical Material

For purposes of this paper all cases of aortic stenosis without evidence of incompetence were studied, regardless of whether other valve lesions were present, provided the subject was under 50 years of age. In addition to the fifteen cases seen personally, the more recent records of the National Heart Hospital were examined and the notes of a further twelve cases abstracted. It has not been found possible to complete the findings in any case by autopsy.

The main points in the history of these cases are summarized in Table I. The fact that twenty of the twenty-seven cases were males is in accordance with other lesions of the aorta and aortic valve. The age incidence was evenly distributed from the age of five years upwards. Most patients gave a history of known or suspected heart disease of many years duration, in twelve over ten years and in eight of these over twenty years. In spite of this only eight presented with symptoms, and these facts agree with the recognized benign nature of aortic stenosis and the consequent late development of symptoms. Of eight patients who were eligible, five served for long periods in the recent war, this also indicating the ease with which the condition may be overlooked. Of the twenty-seven cases, twenty-six denied any history of a rheumatic illness. The remaining one suggested that he had had rheumatic fever in childhood, but interrogation of the parents made this unlikely—an important fact for further consideration.

The physical signs displayed in the fifteen cases seen personally are summarized in Table II. In most cases the cardiac impulse was of normal character, so that palpation confined to the mitral area would not lead to any suspicion of heart disease. In one only (14) was the cardiac impulse certainly abnormal, though four others were suspicious because of its forcible character. Even so a systolic thrill was present in the aortic area in every case, though in five it was only just appreciated with the patient leaning forward, after exertion and in full expiration. That such a thrill could be

TABLE I

AGE INCIDENCE AND HISTORY IN PURE AORTIC STENOSIS (A.S.)

Case No.	Sex	Present age	Age A.S. confirmed	Age heart suspected	Length of history (years)	Mode of discovery	Army service (years)
			Cases seen personally				
1	M	11	10	5	6	School	—
2	M	11	11	5	6	School	—
3	M	12	11	3	9	School	—
4	F	20	20	8	12	School	—
5	M	24	24	18	6	Med. Board	—
6	M	26	26	2	24	Routine	—
7	M	29	29	9	20	Insurance	4
8	M	31	30	30	1	Civil Service	6
9	M	34	34	23	11	Med. Board	—
10	M	36	35	35	1	Symptoms	4
11	M	36	36	10	26	Routine	6
12	M	39	39	11	28	Symptoms	3
13	M	42	40	12	30	Routine	—
14	F	47	36	15	32	Symptoms	—
15	F	49	49	49	—	Symptoms	—
			Cases from the records				
16	M	—	5	Birth	5	—	—
17	M	—	11	5	6	—	—
18	F	—	23	?	?	—	—
19	F	—	25	5	20	—	—
20	M	—	25	12	13	—	—
21	F	—	26	21	5	—	—
22	M	—	28	10	18	Symptoms	—
23	M	—	31	29	2	Symptoms	—
24	M	—	39	39	—	—	—
25	F	—	42	6	36	Symptoms	—
26	M	—	47	47	—	—	—
27	M	—	48	39	9	Symptoms	—

TABLE II

PHYSICAL SIGNS IN PURE AORTIC STENOSIS

Case No.	Character of cardiac impulse*	Aortic Systolic thrill	Character of second sound	Blood pressure
1	Forcible	Present	Normal	100/75
2	Forcible	Present	Normal	120/90
3	Normal	Present	Normal	90/70
4	Forcible	Present	Diminished	115/90
5	Normal	Present	Normal	135/110
6	Normal	Present	Diminished	120/80
7	Normal	Present	Normal	135/95
8	Normal	Faint	Normal	135/90
9	Normal	Present	Diminished	130/90
10	Normal	Faint	Normal	120/80
11	Normal	Present	Normal	130/90
12	Normal	Faint	Normal	125/85
13	Not palpable	Faint	Normal	130/80
14	Heaving	Faint	Diminished	140/95
15	Forcible	Present	Normal	140/90

There was no evidence of a mitral lesion in any case.

* The position of the cardiac impulse was normal in all cases except in Case 14 where it was slightly displaced and perhaps in Case 13 where it was not felt.

easily missed is not surprising. Naturally, there was always a corresponding harsh or rough systolic murmur heard in the aortic area and also in the mitral area, the intensity varying from case to case. The second heart sound, as heard in the aortic area, was normal in character in eleven and diminished in the remaining four, being easily audible in every case. After auscultation in various positions and after exertion, there was no evidence of mitral stenosis in any case, and this evidence would include not only the presystolic and mid-diastolic murmurs, but a loud first sound and the sound heard in early diastole variously ascribed to the third heart sound, the opening snap of the abnormal mitral valve, or splitting of the second heart sound. In the presence of aortic stenosis the systolic murmur in the mitral area must be attributed to the aortic valve and cannot be used as evidence to incriminate the mitral valve: the absence of a mid-diastolic murmur is of greater significance for there is no early diastolic murmur, so frequently well heard in the mitral area in aortic incompetence, to confuse the issue. The blood pressure showed no great departure from the normal.

X-Ray Findings

Each of the fifteen cases was screened in the three orthodox positions. Summarizing, there would appear to be three important abnormalities, cardiac enlargement, prominence of the ascending aorta, and calcification of the aortic valve. Radiological evidence of cardiac enlargement was considered to be absent in only one case but in twelve others it was assessed as slight. In only two was it considered more than slight, and then only moderate. Enlargement was confined to the left ventricle in all and was judged more by increased convexity of the left ventricular border than by apparent increase in the surface area of the cardiac silhouette. The detection of lesser degrees of cardiac enlargement is a difficult radiological problem and in the group under discussion it is always so, for cardiac enlargement must be attributed rather to hypertrophy than dilatation so that the size-weight ratio is small compared for instance with corresponding degrees of aortic incompetence. More striking than the slight grade of cardiac enlargement, and easier to detect with certainty, was the increase in width of the aortic shadow, bearing in mind the comparative youth of this group of patients and the absence of hypertension. An example is given in Fig. 1. This was noted in all but one, to a greater or lesser degree, and was chiefly confined to the region of the ascending aorta. Calcification of the aortic valve was noted in eight of the fifteen cases. Finally, there was no radiological support for a diagnosis of mitral stenosis in any case.

Electrocardiographic Findings

The standard limb leads, and in addition multiple chest leads (CR or V) and the unipolar limb leads, were recorded in all cases. Of the fifteen studied twelve came within the normal limits, so that there was no evidence of left ventricular preponderance. The three showing left ventricular preponderance were Cases 4, 6, and 14. Case 4 showed a normal axis with high voltage R waves and depression of the R–T segment with deep inversion of T in the standard limb leads. There were similar changes in the chest leads facing the left ventricle, i.e. V5 and V7. The electrical axis was vertical in type as shown by the unipolar limb leads and the characteristic changes of left ventricular preponderance were seen in the lead facing the left ventricle, i.e. VF (Fig. 2A). Case 6 showed a normal axis in the orthodox leads accompanied by high voltage R waves followed by depression of the R–T–T complex in II and III. Similar changes were seen in V6 and VF, the electrical axis being vertical (Fig. 2B). Case 14 showed the orthodox type of left ventricular preponderance so that in the presence of left axis deviation there was depression of the R–T segment with inversion of T in leads I and II. Similar changes were present in leads V7 and VL, so that the electrical axis was horizontal (Fig. 2C). This case has been under observation since 1936 and in that year the axis was normal according to the orthodox leads with depression of R–T and inversion of T in II and III. In the intervening period there has obviously been a change in position of the electrical axis from a vertical to a horizontal position.

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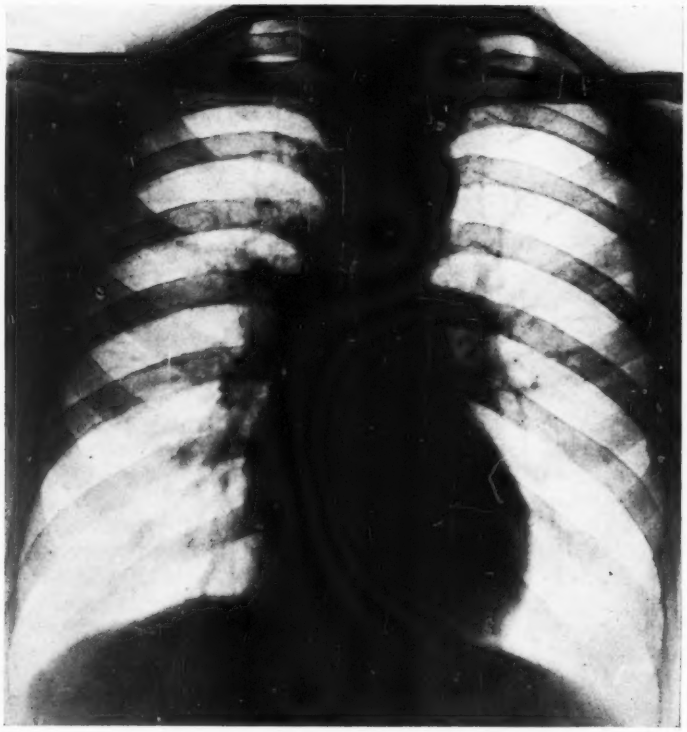

FIG. 1.—Case 8. Postero-anterior view showing prominence of the ascending aorta and increase in convexity of the left ventricular border. These features were more apparent on screening, which also revealed aortic valvular calcification.

Of the twelve cases that were considered normal four presented a vertical type electrical axis so that six cases in all belonged to this category, only one of which was in a child. One of these (Case 5) showed some right axis deviation in the standard limb leads with upright TII and deep inversion of TIII (Fig. 3).

Phonocardiographic findings. A phonocardiographic record using the electrocardiogram as the reference tracing was made in five cases and one is shown in Fig. 4. In four there was no evidence of a murmur in early diastole and in none was a presystolic or mid-diastolic murmur recorded, so that phonocardiographically the clinical condition of pure aortic stenosis was confirmed. Doubt has previously been cast upon the idea that aortic stenosis can be pure for the suggestion has been made that it will always be associated with a murmur in early diastole even though it is not always audible.

DISCUSSION: ÆTIOLOGY

In such an age group the question naturally arises as to the part that rheumatic infection may or may not play in the causation of this type of aortic stenosis. The history in this series gives no support at all. As a contrast, in a series of forty-one cases of aortic stenosis and incompetence taken at random from the records of the National Heart Hospital twenty-four (60 per cent) gave a

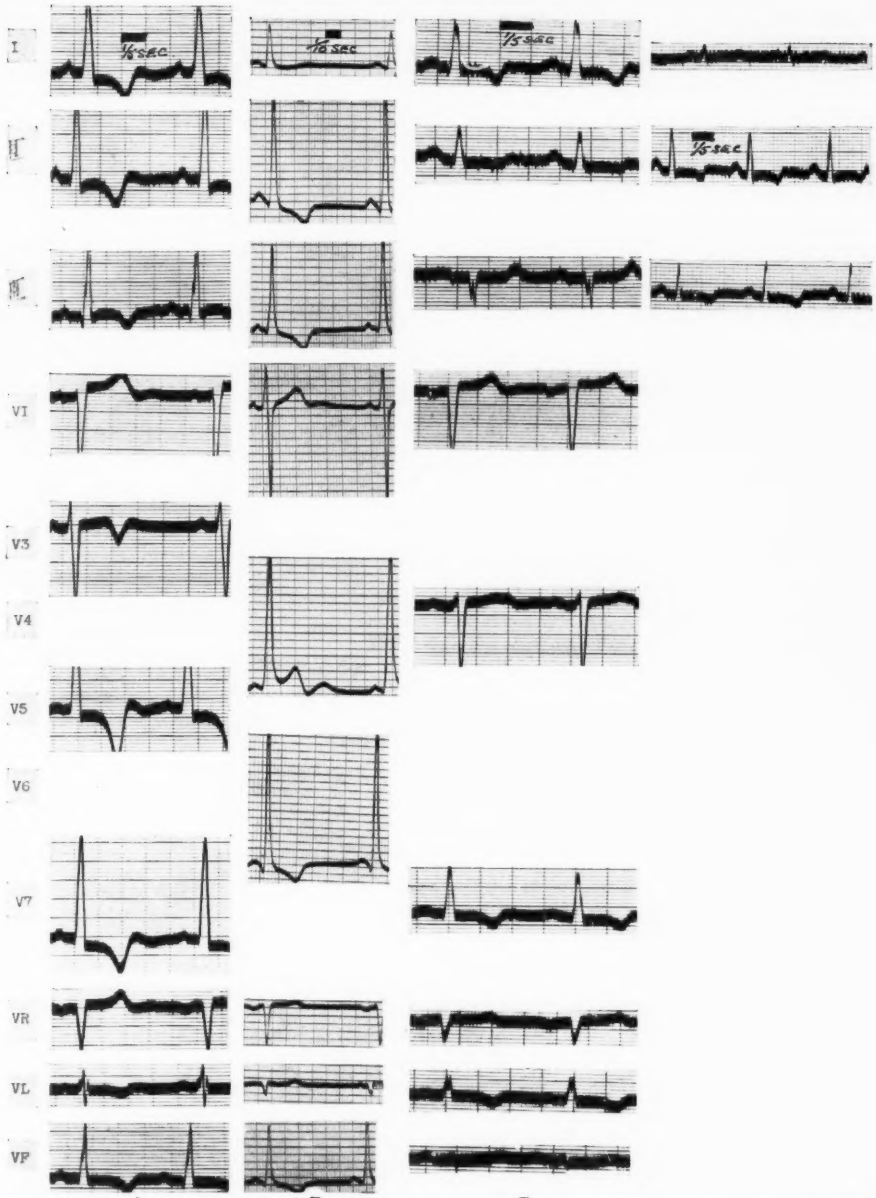

FIG. 2.—(A) Case 4. Left ventricular preponderance with high voltage normal axis in the orthodox leads. The chest leads confirm the ventricular preponderance, and the unipolar limb leads show that the electrical axis is vertical. (B) Case 6. Similar changes in Case 5; see Fig. 3. Here the T in lead I is isoelectric. (C) Case 14. In 1948, showing orthodox evidence of left ventricular preponderance, the unipolar limb leads confirming that the electrical axis is horizontal. The tracings taken in 1936 show that there has been a change in the axis which was then apparently of the vertical type.

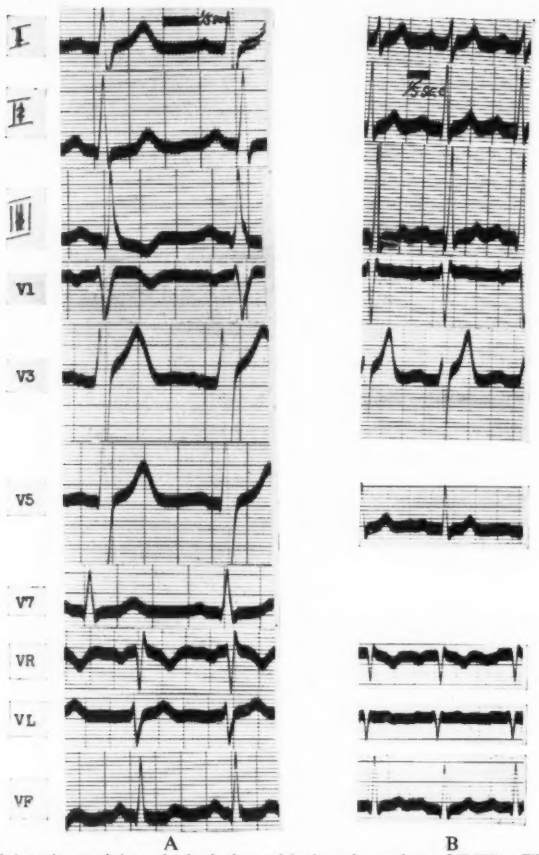

FIG. 3.—(A) Case 5. High-voltage right axis deviation with deep inversion of T III. The T over the right ventricle is tall and the T in VF is lower than the T in VL. The electrical axis is vertical as shown by the unipolar limb leads. Probably a normal curve. This patient had well marked calcification of the aortic valve. (B) Case 9. High-voltage right axis deviation with tall T over the right ventricle and vertical electrical axis. This patient had well marked calcification of the aortic valve.

rheumatic history, and in 104 cases of aortic incompetence and mitral stenosis, sixty-one (nearly 60 per cent) had a history of rheumatic infection. These percentages are minimal, for in some the history was not recorded. In addition to the absence of a rheumatic history, each patient was assessed for evidence of mitral stenosis including radiological examination and in none did this exist. For what it is worth the author cannot remember a case of pure aortic stenosis associated with mitral stenosis: and in studying the records of forty-one cases of aortic stenosis with mitral stenosis only three were found in which there was a possibility of the aortic stenosis being pure—the notes being incomplete in each—the three patients in question were aged 57, 62 and 65 years, so that they were outside the age limit under consideration.

So far the evidence in favour of a rheumatic basis for this type of aortic stenosis is completely lacking, but the argument has been used that rheumatism is responsible, the heart having almost escaped, except that the aortic valve alone has been " touched " and in the course of years has become increasingly calcified with resulting stenosis. Parkinson and Hartley (1946) discussed a series of 202 cases of aortic incompetence in service recruits, and though the majority were slight

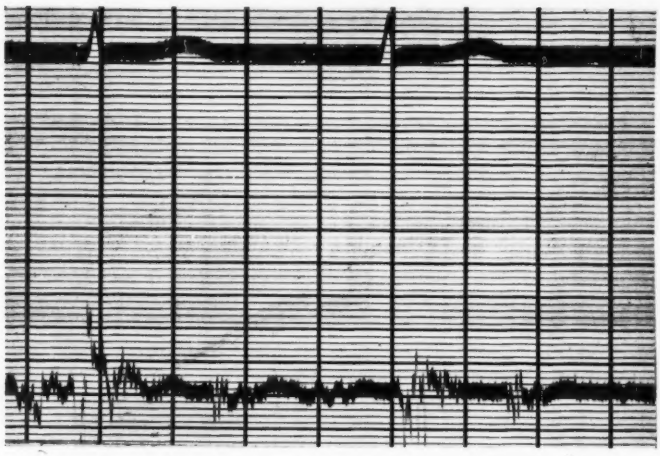

FIG. 4.—Case 3. Phonocardiogram showing murmur in systole but no early or other murmur in diastole.

in degree, ninety-eight (nearly 50 per cent) gave a rheumatic history. These cases in the main had no symptoms and no peripheral vascular signs, and surely result from an infection that has just " touched " the aortic valve: in spite of this a very high percentage gave a rheumatic history. A paper by Young (1944) lends unintentional support to a non-rheumatic basis: under the heading *Congenital Sub-Aortic Stenosis* he described ten cases picked up in 18,000 recruits, but it is clear from the clinical study that they presented the same clinical picture as those described in this paper, with no history of rheumatic infection and no evidence of mitral stenosis. Less than forty proven cases of sub-aortic stenosis have been reported, and this fact, coupled with the identical physical signs, supports the probability that all Young's cases were examples of pure aortic stenosis. If this be so, he misinterpreted the physical signs, so that here is another series of pure aortic stenosis without any history of rheumatic infection and no evidence of a mitral lesion. It is reasonable to assume that had others with the same signs presented with a history of rheumatic infection or evidence of a mitral lesion the non-rheumatic cases would not have been described as examples of sub-aortic stenosis.

Perhaps the strongest support for a rheumatic basis comes from the recent monograph of Karsner and Koletsky (1947) who conclude that calcific aortic stenosis is always of rheumatic origin. They investigated 200 cases coming to autopsy and their results show that with only rare exceptions, calcific disease of the aortic valve is the result of rheumatic cardiac disease. Of the 200 cases, four could not be shown to be rheumatic. The type of aortic stenosis described in this paper is certainly uncommon though it is not rare, and its incidence might well be covered by the 2 per cent of cases that Karsner and Koletsky failed to demonstrate to be rheumatic. It has also been suggested by Hall and Anderson (1943) that the incidence of rheumatic fever in the human race is comparable to that of tuberculosis and infantile paralysis. Should this be so, then the value of microscopy in the proof of valvular disease being of rheumatic origin will be diminished considerably and even a greater percentage of cases of aortic stenosis may be non-rheumatic than shown by Karsner and Koletsky, who relied largely upon microscopic findings for their results.

Gallavardin, in his three clinical papers, held strongly to the view that this group is non-rheumatic; he described fifty cases and considered that they followed a non-specific inflammatory condition resulting in chronic endocarditis acquired in infancy or early adult life. He also stated that rheumatic aortic stenosis will always be accompanied by some degree of incompetence. This opinion is shared more recently by Taussig (1947), who states that " the insidious development of

aortic stenosis of rheumatic origin without aortic insufficiency or involvement of the mitral valve is so rare that it is virtually non-existent."

To sum up, the evidence is in favour of this type of aortic stenosis being of non-rheumatic origin, though there is no autopsy evidence to support this view. The lesion is benign, allowing gross calcification to occur before causing death, and probably in the later stages incompetence will occur, as a result of increasing deformity of the cusps. Microscopically, at this stage, it is likely that the valve is indistinguishable from that of rheumatic origin, and unless investigated by a pathologist trained in this particular field, will certainly be regarded as rheumatic The answer to this problem can only come from a " follow-up " confined to this type of case over many years to the autopsy room. Even then the most valuable information would only come if the subject died from accident or intercurrent disease, so that the lesion could be examined at a relatively early stage.

If this type of aortic stenosis is not of rheumatic origin the question of a congenital origin has to be considered. The diagnosis of sub-aortic stenosis is frequently put forward when this combination of physical signs occurs, as was done apparently by Young, and this is the combination of signs that theoretically might be expected when the condition is uncomplicated. Less than forty examples of this lesion have been confirmed at autopsy, so its rarity must be accepted and therefore it cannot be lightly diagnosed. Support for the view that sub-aortic stenosis does not lend itself to clinical recognition is met by approaching the problem from another angle and examining the records of reported cases and noting whether in fact they did present these signs. The details of sixteen of these cases have been abstracted and are set out in Table III. Of the sixteen cases there are twelve

TABLE III

REPORTED CASES OF SUB-AORTIC STENOSIS

Author	Age	Clinical diagnosis	Auscultatory signs	Autopsy findings
Banks, 1857	34	Aortic incompetence	Loud early diastolic murmur	Aortic valve thickened; cribriform
Lindman, 1880	19	Coarctation of aorta	Aortic S. thrill and mitral M.D.M.	Aortic valve normal
Moore, 1883	18	—	—	Aortic aneurysm, aortic valve normal
Trevor, 1901	9	—	—	Mitral stenosis
Smart, 1904	17	Aortic incompetence	Loud lung D.M.	Aortic and mitral stenosis
Shennan, 1905	19	Aortic stenosis	A.S. thrill and murmur	Aortic stenosis
Thursfield and Scott, 1913	14	Ventricular septal defect	Loud long Aortic S.M.	Aortic stenosis
Lemierre and Bernard, 1925	18	Aortic stenosis Mitral stenosis	Aortic and mitral S. thrill and murmur P.S.M. M.D.M.	Aortic and mitral stenosis
Enzer, 1927	40	Mitral incompetence	M.S. thrill and murmur	Aortic stenosis
Sternberg, 1930	27	Aortic stenosis	—	Aortic valve normal
Sternberg, 1930	77	—	—	Calcific aortic stenosis
Stewart and Bellet, 1934	26	—	Mitral S. murmur	Coarctation of aorta
Wiglesworth, 1937	8	Cong. morbis cordis	Mitral S. thrill and murmur	Aortic stenosis
Dormans, 1939	16	—	Systolic murmur	Aortic stenosis
Mason and Hunter, 1943	27	Aortic stenosis (calcific) Sub-aortic stenosis	Aortic S. thrill and murmur A2+	Aortic stenosis
Walsh, Connerty and White, 1945	27	Aortic stenosis and incompetence	Loud rough aortic S. thrill and murmur blowing D.M. A2 dim.	Aortic stenosis

in which the auscultatory signs are given in some detail and these do not agree with theoretical expectation as in only two cases was the lesion an isolated one. In one of these a mid-diastolic murmur was recorded and the physical signs were not mentioned in the account of the other. In only five cases was the aortic valve apparently normal, so that in eleven, aortic valvular stenosis of varying degree was noted. Mason's case was diagnosed in life because of the clear-cut second

sound, absence of an aortic diastolic murmur, and evidence of aortic obstruction. As he at the same time diagnosed " calcific (probably) aortic stenosis," it is difficult to follow his reasoning that the subvalvular lesion was also present. It is a diagnosis not uncommonly offered, and rare though it is, will sooner or later prove to be correct. It would seem reasonable to assume that the condition cannot be recognized in life and that a more accurate diagnosis than aortic valvular stenosis is not possible in the present state of knowledge. When it does occur the chance of it presenting the signs given by the group of cases described above is small and it must be assumed in practice that all such cases have aortic valvular stenosis.

There are other possibilities of a congenital origin for this type of case. Koletsky (1941) has shown that a congenitally bicuspid valve may in the course of years undergo calcification; at the same time he regards this lesion as the most common single congenital cardiac anomaly. This might be expected to give rise to stenosis of varying degree. True congenital aortic stenosis is a well recognized though infrequent lesion, but can only be diagnosed with confidence when the characteristic signs are detected within the first three years of life. Does not the possibility exist of slighter degrees of this condition giving rise to no signs at birth or an early age, until later calcification takes place and results in stenosis? Finally, there is no knowledge of what may happen to a fenestrated aortic valve and whether it may become calcified. If any of these congenital possibilities exist it is likely that when death occurs, the precipitating cause will no longer be apparent because of extensive calcification and deformity.

Apart from these considerations it has been suggested that healed bacterial endocarditis may explain a diagnosis of aortic stenosis of non-rheumatic origin. In these days of penicillin this becomes increasingly possible, but certainly does not apply to the cases under discussion. Such a view has been described by Willius and Dry (1939) as fantastic.

Finally, there is the view of Gallavardin as described above, but all these theories remain theories in the absence of post-mortem evidence in this type of case.

Clinical Signs

It has been traditionally taught that there are five abnormal physical signs to be sought before a diagnosis of aortic stenosis is justified. These are (*a*) a systolic thrill in the aortic area, (*b*) a long harsh or rough systolic murmur in the aortic area, (*c*) diminution or absence of the second sound in the same area, (*d*) evidence of left ventricular hypertrophy, and (*e*) alteration in the character of the peripheral pulse wave, i.e. pulsus bisferiens or pulsus anacroticus. Because of too strict adherence to some or all of these criteria lies the probable reason why aortic stenosis is so frequently missed in diagnosis, a fact that has been pointed out by several writers and more particularly by Karsner and Koletsky. Excluding examination of the peripheral pulse wave (which clinically is so much a matter of opinion) the present group of cases in the main only exhibited two of these signs, i.e. the thrill and murmur, and the former was often difficult to elicit. The most constant and reliable sign, therefore, was the long harsh or rough systolic murmur in the aortic area. It is interesting to recall that both Willius (1939) and White (1944) regard a murmur of maximal intensity in the aortic area as almost always organic and due to disease of the aorta or aortic valve. In this connection Willius states: " I have had the opportunity to examine numerous patients in whom the detection of an aortic systolic murmur many years before had been disregarded and said to be of no significance. Among these patients were some veterans of the World War who were unequivocally accepted for active service in spite of the recognition of an aortic systolic murmur. The ensuing years proved my contention of the significance of this murmur as the patients under discussion all presented well marked calcareous stenosis of the aortic valve at the time of my examination 15–20 years later." The cases described by Willius are similar to the group described in this paper and of the five patients who served for long periods on active military service four have been shown to have a calcified aortic valve.

The importance of diminution or absence of the aortic second sound in aortic stenosis has for

long been stressed. Dry and Willius (1939) regard the preservation of the second sound in this condition as indicative of the dynamic function of the cusps and as an indication therefore that the degree of stenosis is mild or moderate. They also believe that in aortic stenosis the second sound in the aortic area may be normal as do McGinn and White (1934) and others. In this series the second sound was considered to be normal in eleven of the fifteen cases and in six of these the valve was radiologically calcified. Not only may the aortic second sound be normal in aortic stenosis but it may be normal even in the presence of radiological calcification. In these cases it is reasonable to believe that the deposit of calcium must be in the neighbourhood of the aortic valve ring, leaving the cusps comparatively healthy. The intensity of the second sound is probably of value in assessing the degree of aortic stenosis and it would seem that this may be fairly considerable in the presence of a normal second sound.

Clinically, the size of the heart may be estimated by two factors: the position of the cardiac impulse and its character. In this series of cases, in the majority, both the position of the impulse and its character were within normal limits.

Radiology

Only two of these fifteen cases showed conclusive evidence of left ventricular enlargement. In one there was no such evidence and in the remainder it was considered to be slight. When radiological evidence for ventricular hypertrophy is slight it becomes very much a matter of opinion whether it is present or not. When cases in which an aortic systolic murmur is the principal sign are being assessed, such equivocal evidence in support of a diagnosis of aortic stenosis should be confirmed if possible by other and more reliable signs. Prominence of the ascending aorta was noted frequently in this series in the postero-anterior and left oblique views. This was often striking and was easier to assess with certainty than any change in the cardiac contour: there is good reason, therefore, to regard it as a sign of greater importance as it is easier to detect. The fact that the aorta immediately above a stenosed aortic valve is dilated would not appear to be commonly realized and is not discussed as an aid to diagnosis in such cases. Perhaps this is because the majority of cases of aortic stenosis are not pure and any prominence in the ascending aorta is attributed to the presence of incompetence. It should not be surprising that the ascending aorta is dilated in such circumstances, as the pulmonary artery is frequently so in the corresponding condition of pure pulmonary stenosis, and it is reasonable to assume that the mechanism is the same in both types of case. If an artery be partially constricted, dilatation of the vessel will occur immediately beyond the stricture and it is likely that the post-stenotic dilation in aortic and pulmonary stenosis is related to this. In aortic stenosis there is the additional factor that the aorta is not straight, so that the stream of blood passing through the stenosed valve at a high velocity is likely to impinge upon the right wall of the ascending aorta, opposite the aortic valve, causing it to bulge in systole. On this theory it is likely that the dilatation of the ascending aorta in pure aortic stenosis is directly proportional to the degree of stenosis. There is some pathological support for this view. Hall and Ichioka (1940) have reported " impingement plaques " of the aorta in severe aortic stenosis, the aorta being otherwise unusually healthy considering the age of the subject. The plaque is an atheromatous lesion situated in the median-posterior aspect of the ascending aorta 6–8 cm. long and 1–1·5 mm. wide. Although these plaques do not seem to be reported by others, they suggest that extra stress is taken by that part of the aorta diametrically opposite the aortic valve.

Intra-cardiac calcification in the neighbourhood of the aortic valve was present in eight of the fifteen cases and the search for this may therefore be helpful and important. In seven, the presence of cardiac enlargement was a matter of opinion, whereas there could be no doubt about the valvular calcification. It is the dynamic movement of the dancing intra-cardiac shadows that is convincing in the recognition of this condition, so that the radioscopy is more helpful than radiography. Another sign was sustained pulsation of the aorta, but this could only be detected in a small number of the more severe cases where the condition was easily recognized by other means.

In the diagnosis of pure aortic stenosis the best radiological evidence is undue prominence of the ascending aorta and calcification of the aortic valve.

Electrocardiography

Of the fifteen patients studied, eleven were electrocardiographically normal. From a prognostic point of view this is not surprising and is in accordance with the freedom from symptoms which these patients enjoy.

In six cases a vertical electrical axis was present, and five of these were adults. In the standard leads there was a normal axis or right axis deviation and the true axis was shown by the use of the unipolar limb leads. There was nothing in the body build of these patients to make one expect this, but it seems to be common in aortic valvular disease. This cannot support the belief that mitral stenosis was present, for right axis deviation is not inconsistent with left ventricular hypertrophy, as has been shown by the work of Wilson and Goldberger. The pattern of left ventricular preponderance is then altered: for whereas with the orthodox type (with left axis deviation) depression of the R–T–T complex begins and is greatest in lead I; with the electrical axis of the vertical type (with normal or right axis deviation in the standard leads) R–T–T depression may be present in all three leads or may begin and be most marked in lead III. Examples are shown in Cases 4 and 6 as described above, and Case 14 is an example of the common or orthodox type of left ventricular preponderance with left axis deviation and formerly (in 1936) was an example of the less common type, there being a change of the position of the electrical axis in the intervening years.

Summary

Fifteen patients with pure aortic stenosis, all under the age of 50 years, are described, together with a review of the history of a further twelve patients taken from hospital records.

The ætiology is discussed and there is general agreement with the conclusions of Gallavardin that rheumatic infection cannot be the responsible agent. Other possible causes are discussed but there can be no final answer in the absence of autopsy investigation. Because of the physical signs presented in this group the diagnosis of sub-aortic stenosis is often advanced, but cannot be substantiated here; it is suggested that this condition cannot be recognized in life though it is possible that angiocardiography may assist in future. A long-term investigation confined to this type of case is necessary before the answer to this ætiological problem is obtained.

The physical signs are briefly discussed and the combination, characterized as it is mainly by a systolic murmur in the aortic area, is one that can be and is easily overlooked. The second sound in the aortic area is often normal, even in the presence of calcification of the aortic valve.

The radiological evidence shows that cardiac enlargement is generally slight, and therefore not convincing to all. In the assessment of cases presenting with an aortic systolic murmur, the importance of prominence of the ascending aorta and calcification of the aortic valve in support of a diagnosis of aortic stenosis is stressed.

Electrocardiograms showed evidence of left ventricular preponderance in only four of the fifteen cases studied so that this could not be relied upon to assist in the diagnosis. Of these, three showed a vertical type electrical axis and because of this the evidence in support of ventricular preponderance was not of the orthodox kind. There were six cases that showed a vertical electrical axis and it is believed that this is not uncommon in aortic valvular disease.

Phonocardiographic evidence showed that aortic stenosis can be pure.

With no symptoms, minimal cardiac enlargement, and normal electrocardiographic tracings, it is likely that many of these patients will survive to the age when atherosclerotic aortic stenosis becomes a consideration in diagnosis. Many of these were discovered by accident, and had no symptoms. Had this fortuitous happening not occurred, the diagnosis might have had to wait for

the development of symptoms, which might well have been past the age of 50 years. The relationship between this type of aortic stenosis and the calcific aortic stenosis of elderly people may be a close one.

I wish to thank the members of the Staff of the National Heart Hospital and Institute of Cardiology for permission to study patients under their care; without their help and encouragement this paper would not have been possible. I also wish to thank Dr. William Evans for his permission to reproduce the phonocardiogram which is one of several that he kindly recorded for me.

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THE PROBLEM OF EXCESSIVE RADIATION DURING ROUTINE INVESTIGATIONS OF THE HEART

BY

T. H. HILLS AND R. W. STANFORD

From the Diagnostic X-ray Department, Guy's Hospital

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Angiocardiography and cardiac catheterization have produced many new problems in radiology, and it is most important that both the cardiologist and radiologist should be aware of the dangers to which they may expose themselves and their patients. For example, in designing apparatus for angiocardiography it must be borne in mind that if this procedure is used for routine investigations care must be taken beyond that necessary in experimental work, since it is essential that all concerned should be adequately protected from both direct and scattered radiation. Unfortunately a knowledge of the output of the X-ray set, in terms of kilovoltage and milliampere seconds, is insufficient to enable the quantity of radiation received by the patient and those in close proximity to the patient to be calculated. In this paper an attempt is made to show what factors must be considered in estimating the direct and scattered X-rays, and to give some indication as to how this estimation can be carried out. Little has been published in the past about the measurement of scattered radiation in diagnostic X-ray work, and the recommendations set out in the following paragraphs are based on experiments carried out in the X-ray Department at Guy's Hospital during investigations of routine cases.

The measurements recorded in the following paragraphs were made with two main objects in view, (*a*) to ensure that the patient does not receive an excessive dose; and (*b*) to protect those near to the patient. Whereas the risk to the patient lies in administering a dose of X-rays sufficient to cause burning of the skin, the danger to those nearby arises from the fact that they are frequently exposed to radiation and must be protected from its long-term effects, viz. injury to the superficial tissues, and changes in the blood and bone marrow and reproductive organs. With the average quality of the X-ray beam used for these investigations, that is filtered by one millimetre of aluminium or its equivalent in other ways, the dose that will produce a first-degree erythema of the skin is about 150 rontgen units* delivered on one day. In connection with the filtration of the beam it is useful to note that an aluminium filter is necessary for safety and such a filter or its equivalent is frequently incorporated during manufacture. The purpose of this is to suppress the very soft radiation from the tube since such radiation is particularly harmful. The filter does not eliminate the risk of burning referred to previously, nor does it give any indication of the dosage. The maximum permissible whole body dose for persons who are regularly exposed to radiation, such as the radiologist, surgeon, and anæsthetist, has been fixed as 0·5 r. per week, or a dosage rate of 4×10^{-6} r. per second. For the hands, informed opinion tentatively regards 1·5 r. per week as the maximum permissible dose. At the outset we wish to emphasize the fact that although these investigations are diagnostic procedures nevertheless it is quite possible for the patient to receive a dose sufficient to cause a first-degree erythema and for those nearby to receive a dose well in excess of the permitted maximum. Further-

* The rontgen (r.-unit) is a unit of dosage for ionizing radiations and is based on the ionization produced by the radiation in air under standard conditions.
In this paper the abbreviation r. denotes rontgen.

more the potential injury is caused to the patient by the direct beam; but to those nearby, mainly by radiation scattered from the patient.

The arrangement of apparatus employed for routine cases of angiocardiography has already been described by Hills (1948), and that for cardiac catheterization by Holling and Zak (1950). Using these methods, observations have been made both during treatment of patients and by using a wax phantom to simulate the patient. For the determination of doses the instruments used were a Victoreen dosemeter, a pocket type Lauritsen dosemeter, and a small condenser ionization chamber with a Baldwin Farmer electrometer. A Philips D.X.4 set was used for angiocardiography and a G.E. Victor set for the catheterization.

Angiocardiography

Fig. 1 shows the relative positions of patient, tube and camera. Points X and Y indicate the approximate positions of the surgeon and anæsthetist.

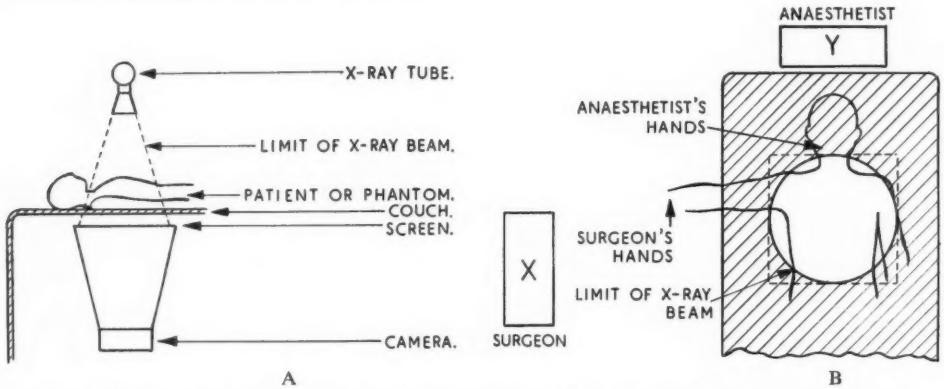

FIG. 1.—Diagrams of position of patient, tube and camera and the relative positions of surgeon and anæsthetist. (A) Side view. (B) Plan view.

A short focus screen distance was largely dictated by the need for obtaining the brightest shadow on the screen, and in practice this distance was set for 30 inches. It was of course arranged that the X-ray beam should cover only the area of the fluorescent screen that was photographed by the camera. The settings for the tube were generally in the range 70–77·5 kilovolts, 300–400 milliamperes, and 0·1 seconds for A.P. views. For oblique views the kilovoltage was increased to 80–85. For the purpose of taking measurements the settings (nominal) employed were 77·5 kilovolts, 400 milliamperes, and 0·1 seconds.

The radiation dose at the level of the skin of the patient, but without a patient in position, was found to be 1·1 r. per exposure. When a wax phantom was inserted in the position which would be occupied by the patient the dose was 1·5 r. per exposure. This difference is due to the fact that when the direct beam enters the phantom (or patient) some of the radiation is scattered. A proportion of this radiation is scattered back towards the tube and emerges at the surface of the phantom (or patient) where it reinforces the direct beam. The total dose at the surface thus comprises incident plus scattered radiation and is termed the " skin dose." Over the whole irradiated surface this skin dose varies from 1·0 r. at the perimeter of the field to 1·5 r. at the centre. Thus the average skin dose per exposure may be taken as 1·3 r.

Observations of scattered radiation were made at various points in space round the phantom. For convenience the values quoted are those showing the variation (*a*) along the horizontal direction coinciding with the outstretched arm of the patient, (*b*) along the vertical directions at a distance

corresponding with the approximate position of the surgeon, and (*c*) along the vertical direction at a distance corresponding with the approximate position of the anæsthetist. These are summarized in Table I.

TABLE I

SCATTERED RADIATION AT VARIOUS POINTS ROUND THE PATIENT

Distance in cm. from centre of patient along arm	Dosage in rontgens per exposure
18 (Side of patient)	1·6
25 (Edge of table)	0·13
45 (Approx. position of surgeon's hands)	0·020
55 (Approx. position of surgeon)	0·012

Distance in cm. above or below level of patient at a horizontal distance of 55 cm. from patient (i.e. approx. position of surgeon)	Dosage in rontgens per exposure
+55 (Position of head)	0·014
−15 (Position of pelvis)	0·013

Distance in cm. above or below level of patient at a horizontal distance of 40 cm. from patient (i.e. approx. position of anæsthetist)	Dosage in rontgens per exposure
20 (Position of head)	0·025
−40 (Position of pelvis)	0·027

During the course of a number of investigations a small condenser chamber was placed inside the surgeon's glove to record the dose received at the back of his hand. These readings varied from 0·1 r. to 1·0 r. for a complete series of exposures, the most frequent value being 0·2 r. The dose was closely related to the size of the patient and hence to the distance of the hand from the patient (see Table I). Measurements were also made to determine the dose received by the anæsthetist's hands, the position of which depends on the size of the patient. In practice only young patients are anæsthetized and of necessity the hands are always on the fringe of the direct beam and frequently directly in the beam. Observations showed that the dose received by the back of the hands could vary from 0·82 r. on the fringe of the beam to 1·5 r. in the beam, per exposure. This latter dose is greater than that received by the patient because the hands are closer to the tube.

All the doses quoted above will vary if kilovoltage, tube current, and/or exposure time varies. The effects of such variations are shown in Table II. It will be noted that the exposure time was fixed at 0·1 seconds since experience showed that this was the optimum time to reduce the blurring due to respiration and still achieve adequate contrast on the films.

Changes in kilovoltage and tube current are made in order to compensate for the variation in size of the patient. Consideration of these figures reveals that the intensity of the scattered radiation does not vary significantly with changes in size of the patient.

CARDIAC CATHETERIZATION

The problem to be considered in this case differed from the previous one in so far as the patient is screened, using the under-couch tube, at a lower kilovoltage and a very much smaller tube current but for a greatly increased length of time. The arrangement of apparatus admits of less variation

TABLE II

VARIATION OF DOSAGE WITH CHANGE OF KILOVOLTAGE AND TUBE CURRENT

Kilovolts	Tube current in milli-amperes	Exposure time in seconds	Dosage per exposure, in rontgens, to						
			Surgeon			Patient. Skin dosage at centre of field	Anæsthetist		
			hands	head	pelvis		hands	head	pelvis
77·5	400	0·1	0·02	0·014	0·013	1·5	1·5	0·015	0·027
70·0	400	0·1			0·012	1·3	to		0·026
82·5	400	0·1			0·015	1·7	0·82		0·030
77·5	300	0·1			0·010	1·1			0·012
70·0	300	0·1			0·008	1·0			0·016
82·5	300	0·1			0·012	1·1			0·026

than for angiocardiography, and in fact the only factor directly controlled by those taking part in the investigation is the position of the diaphragms of the tube. This will be referred to later in the paper.

Before making observations it was necessary to decide on suitable settings for the tube. A time limit of twenty minutes had already been imposed on the grounds of possible harm to the patient, and experience had shown that the screening current could be much reduced whilst still maintaining a suitable contrast on the screen. Nominal settings of 64 kilovolts and 0·5 milliamperes were used for the bulk of the observations. Although the screening current is quoted as 0·5 milliamperes, it must be understood that for purely technical reasons the actual current through the tube differs from this by an amount depending on the particular set used (see later paragraph). In addition the diaphragms were closed down as far as possible, the screen itself being moved when necessary to follow the movements of the catheter. The measured area of cross-section of the beam on the back of the patient was about 12 cm. by 12 cm. For the majority of measurements a wax phantom was used, the phantom being placed about 1·5 cm. above the surface of the couch to allow for the fact that the patient normally rests on a sorbo rubber pad on the couch.

The first observations were to determine the skin dose to the patient. Using 64 kilovolts and 0·5 milliamperes the measured dose rate at the skin was 5·5 r. per minute. This value varies markedly with change of kilovoltage or tube current as can be seen from Table III.

TABLE III

SKIN DOSE OF RADIATION WITH DIFFERENT SCREENING CURRENTS

Kilovolts	Dosage rate at the skin, expressed in rontgens per minute, for nominal screening currents, expressed in milliamperes, of				
	0·5	1·0	1·5	2·0	2·5
52	3·6	5·2	7·0	8·0	9·0
64	5·5	8·5	11·0	13·5	15·0
76	7·0	11·0	15·0	18·5	21·0
88	8·2	13·5	18·6	22·6	27·0

At this point is is necessary to emphasize certain aspects of these data. On the set in use, and in fact or many diagnostic sets, it is not easy to adjust the tube current accurately to 0·5 milliamperes. Further, when the meter reads between 0 and 3·0 milliamperes the registered value cannot be taken as the precise current through the tube. For the apparatus used in these experiments it was possible

to check the actual tube current by putting a meter in the high voltage lead to the anode and comparing its readings with those registered at the control panel. These observations showed that when the control panel meter registered 0·5 milliamperes, i.e. the nominal setting referred to in Table III, the current through the tube was 0·9 milliamperes.

The significance of these facts is that the dosage rates given above, whilst true for the particular equipment, will not necessarily be true for another equipment set up to the same nominal readings of kilovoltage and tube current. An additional factor that will have an effect on output is the inherent filtration of the tube, i.e. the filtering of the radiation from the anode by the walls of the tube and by any other material placed in the path of the beam. When a tube ages, metal from the anode is deposited on the inside of the walls of the tube, and the anode becomes pitted. Both these effects increase the inherent filtration, thus reducing the output. As an example of these factors the output of a tube of identical manufacture but much older and fitted to another equipment with a different control desk was measured. The conditions as far as tube-phantom distance, aperture of beam, etc., were concerned were the same, and the control desk was set to give 64 kilovolts, 0·5 milliamperes as nearly as possible with the controls provided. The dosage rate at the skin was measured as 1·7 r. per minute which is appreciably less than that obtained with the set normally used. Finally, it must be borne in mind that the intensity of X-rays falls off inversely as the square of the distance from the source. The focus—skin distance in the apparatus employed was approximately 40 cm. If this distance were increased to 80 cm. then the tube output would need to be increased fourfold in order to obtain the same brightness at the screen as is used in routine work.

Clearly the criterion to be adopted in deciding upon a suitable setting of kilovolts and tube current must be related to the contrast on the fluorescent screen. In this connection the relative opacity of the catheter is important. For routine investigations at Guy's the catheters used are of American manufacture and have an opaque tip. Other types of catheter may be more or less opaque and will necessitate a suitable adjustment of the tube output. Whatever type of catheter is used, the aim must be to work with the minimum screening current that will suffice to give an adequate degree of contrast on the screen, thus enabling the position of the catheter to be established without ambiguity. The observer must be thoroughly dark-adapted before attempting to judge the suitability of the contrast on the screen.

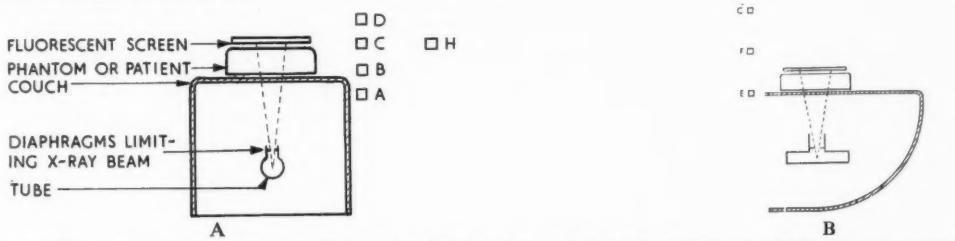

FIG. 2.—Diagram of screen, patient, and X-ray tube with the points marked at which scattered radiation was measured. (A) End view. For A, B, C, D, and H see text and Table IV. (B) Side view. For E, F, and G see text and Table IV.

The measurements made on scattered radiation were carried out in the same manner as for angiocardiography. In this case a fluorescent screen is placed immediately above the patient and this affords a substantial measure of protection in the region of the shadow cast by this screen. The diaphragms are closed as far as possible and this, together with the fact that the lead glass on top of the screen is equivalent to 1·5 mm. of lead under the conditions employed, reduces the radiation passing through the screen to negligible proportions. However, it has been found convenient to use quite a small screen so that the region in space from which radiation is blotted out by the screen is smaller than it would normally be. The results are given in Table IV and the points at which measurements were made are related to Fig. 2 by letters.

To illustrate the reduction in dose rate brought about by increase in distance from the patient, the observation of dose at the level of the surgeon's hands was repeated at a point 20 cm. farther away (see point H in Fig. 2). This point was a total distance of 50 cm. from the centre of the field, and was in the approximate position of the surgeon. At 0·5 milliamperes the dosage rate was 0·003 r. per minute and for 1·0 milliamperes it was 0·0045 r. per minute, a reduction of some 50 per cent from the dosage rate at point C.

TABLE IV

MEASUREMENT OF SCATTERED RADIATION AT DIFFERENT LEVELS

Distance in cm. above or below edge of couch opposite centre of field		Kilovolts	Tube current in milli-amperes	Dosage rate in rontgens per minute
−3, i.e. below edge of couch	A	64	0·5	0·006
		64	1·0	0·014
0, i.e. at edge of couch	B	64	0·5	0·008
		64	1·0	0·011
+10, i.e. approx. position of surgeon's hand	C	64	0·5	0·006
		64	1·0	0·009
+20, i.e. approx. position of surgeon's chest	D	64	0·5	0·008
		64	1·0	0·011
Points higher than this lie in the shadow cast by the screen.				

Distance in cm. above or below edge of couch and 35 cm. along the couch from the centre of the field, i.e. approx. position of radiologist or observer		Kilovolts	Tube current in milli-amperes	Dosage rate in rontgens per minute
0, i.e. at edge of couch and approx. position of pelvis	E	64	0·5	0·0015
		64	1·0	0·003
+20	F	64	0·5	0·003
			1·0	0·009
+40	G	64	0·5	0·005
			1·0	0·009

Any increase in the area of the patient's skin that is irradiated will give rise to two effects. The first of these is that there will be an increase in the skin dose and in the area of the skin affected, the second is that there will be an increase in the intensity of scattered radiation. As an illustration of these effects three measurements were repeated, the skin dosage rate to the patient at 64 kilovolts and 0·5 milliamperes, the intensity of scattered radiation at the position corresponding to the surgeon's hands, and the intensity of scattered radiation at a point corresponding to the surgeon's body, all being taken with the irradiation area increased fourfold. The respective values were 7·2 r. per minute, 0·06 r. per minute, and 0·02 r. per minute, representing a substantial increase.

Observations were taken of the skin dose to the patient and the dose to the surgeon's hands during several catheterizations. These values are in fair accord with the results quoted above, but the measured skin dose is likely to be smaller than that given in the previous paragraph. The reason for this is simply that it is impossible to move the dose measuring chamber about beneath the patient to follow the movements of the screen, and further, the position of the chamber must be at the edge of the field in order to avoid causing any interference with the picture on the screen. The doses given are therefore likely to be smaller than the actual dose received by the patient's skin. In contrast to this it can be seen that the dose to the surgeon's hand is greater than expected; this is almost certainly due to the hand being closer to the patient.

TABLE V

SKIN DOSE TO THE PATIENT AND TO THE SURGEON'S HANDS DURING CARDIAC CATHETERIZATION

Patient	Nominal kilovolts	Nominal tube current in milli-amperes	Screening time in minutes	Skin dose in rontgens	Dose to surgeon's hands in rontgens
A	62	0·5	15½	86	0·22
B	62	0·3	15½	50*	0·65
C	64	0·3	5	34	0·22
D	64	0·5	20	77	0·47

* Measuring instrument at extreme edge of field.

CHEST RADIOGRAPHS

Skin doses were measured for twenty patients using a 6-ft. focus-film distance. With ordinary film the variation was from 0·13 r. to 0·22 r., whilst with special fast film a smaller dose varying from 0·04 r. to 0·12 r. was measured.

ROUTINE SCREENING

The considerations outlined for catheterization in respect of variation in tube output, variation of skin dose with kilovoltage, tube current and screening time, effects of aperture of the diaphragms and focal skin distance and the variation of scattered radiation apply equally in this case. There are, however, certain differences worthy of notice. In a general investigation of this type it is frequently necessary to work with the diaphragms set so as to cover the whole chest instead of a part of it. A brighter screen, requiring a larger tube current is often needed, but the screening time is normally much less than that for catheterization. Observations showed that using a Philips D.X.4 set at 60 kilovolts and 1·5 milliamperes with a focus screen distance of 80 cm., the skin dosage for an average screening time of 3½ minutes was 7·7 r.

DISCUSSION

In assessing the value of these measurements it must be remembered that the observations are certainly not more accurate than ±10 per cent, and in particular that measurements made on one X-ray set are not immediately applicable to another. Nevertheless, the figures quoted do give the correct order of magnitude of the doses, and the conclusions drawn from them do indicate the precautions most likely to be needed to protect the patient and those nearby. It is convenient to review these figures in terms of the patient and those nearby under separate headings.

Patient. There is a risk that he may receive a skin dose sufficient to produce some degree of X-ray burning. It is not thought likely that the total radiation will have any harmful effect otherwise. In considering the effect of X-rays on the skin the time factor must not be omitted, and in assessing the total skin dose all X-ray investigations made must be taken into account since the effects are cumulative. The whole investigation may include ordinary chest films taken at six feet, screening and a barium swallow (probably with further films), screening and further films with cardiac catheterization and an angiocardiography series. The doses on the skin during these investigations are shown in Table VI.

It is obvious that as a diagnostic X-ray procedure one should not approach a skin erythema dose. If a patient has received a dose in the nature of 150 r. he should certainly not have any further radiation to the same area for a period of at least 14 days, and in any year should not receive such a dose on more than three or four occasions at most. Although the tube current for fluoroscopy is fractional in comparison with that used for individual angiocardiographs this aspect of the subject is of no less importance, since it is clear that the greatest dose is that administered during screening.

It is therefore very necessary to decide upon the maximum safe screening time. The most satisfactory method of doing this is to measure the skin dosage rate to the patient under the conditions obtaining during the investigation, and so determine the time during which a dose of 150 r. would be administered. Failing this, it is possible to arrive at an order of magnitude for the skin dosage rate by making use of published data (Binks, 1943) for tube outputs and by assuming that the actual dose at the skin will be increased by a factor of about 20 per cent as a result of back scatter. Hence, again, the maximum safe screening time can be determined. In practice it may well be that the time taken by cardiac catheterization, and therefore the skin dose to the patient, are less than the maximum. If this reduction in dose is appreciable then the time that should elapse before angiocardiography can also be reduced, the extent of the reduction being determined by the actual dose received.

TABLE VI

SUMMARY OF SKIN DOSAGE TO THE PATIENT

Investigation	Skin dosage in rontgens
Chest film	0·04–0·22 r.
Screening and barium swallow ..	7·7 r. for an average screening time of 3½ minutes
	0·6–1·9 r. per film
Screening during catheterization ..	110 r. for a screening time of 20 minutes
	1 r. per film
Angiocardiography series of 10 films..	15 r.
Total skin dosage	136 r. approx.

Those in close proximity to the patient, i.e. surgeon, anæsthetist, and radiologist. The danger incurred by those assisting lies in the regular exposure to radiation. From the figures already given typical whole body doses and hand doses are shown in Table VII.

TABLE VII

SUMMARY OF DOSAGE TO SURGEON, ANÆSTHETIST, AND RADIOLOGIST

Investigation		Dosage
Catheterization	Surgeon—hands	0·12 r. for 20 minutes
	Surgeon—whole body	0·16 r. for 20 minutes
	Radiologist—whole body	0·16–0·60 r. for 20 minutes (depending on position)
Angiocardiorgaphy	Surgeon—hands	0·20 r. for 10 films
	Surgeon—whole body	0·13 r. for 10 films
	Anæsthetist—hands	8·2–15 r. for 10 films (depending on position)
	Anæsthetist—whole body	0·27 r. for 10 films

The above figures refer to one investigation: if the same person carries out more than one a week the dose will increase proportionately.

It will be clear from these figures that the intensity of the scattered radiation is by no means negligible. In fact for the anæsthetist in angiocardiography it is far in excess of the permitted dose, and may easily become so for the surgeon, especially if his hands move into the direct beam. Further, if the same surgeon does two or three investigations a week he then receives a dose

approaching the maximum. Precautions must be taken to ensure safety, and this can be achieved in three ways:

(*a*) by increasing the distance from the source of radiation, i.e. making use of the fact that the intensity falls off as the inverse square of the distance,
(*b*) by the use of protective clothing,
(*c*) by employing lead, lead glass, or lead rubber screening.

From (*a*) it follows that all those concerned should be as far as possible from the table. During catheterization the surgeon and radiologist must be very close to the table and can make little or no use of this factor and must rely on other measures. In angiocardiography the position of the anæsthetist is fixed and he too must rely on other protective measures. On the other hand the surgeon can have the patient's arm outstretched and by using a syringe with a long cannula can stand so that his body is 50–60 cm. from the centre of the patient and his hands well out of the direct beam during the actual exposures.

Considering (*b*) it is clear that the surgeon can wear a lead rubber apron, but some form of special glove may have to be devised since it is impossible to make an injection or insert a cardiac catheter whilst wearing lead rubber gloves. In angiocardiography the anæsthetist should undoubtedly wear lead rubber gloves and a lead rubber apron. Experience has shown that the use of lead rubber gloves for the 10 or 15 seconds of the exposures, whilst causing some inconvenience, does not seriously impair the anæsthetist's efficiency. During catheterization the radiologist should wear a lead rubber apron but can dispense with gloves, since his hands are usually resting on, and hence protected by, the screen.

With regard to (*c*), this presents certain difficulties but they are not insuperable and the use of permanent or detachable protective screens has much to commend it since, if suitably designed, they may obviate the necessity for wearing protective clothing. For angiocardiography such protection for the surgeon is quite feasible and could take the form of lead sheet, or lead rubber below the level of the patient, and lead glass, with an aperture for the patient's arm, above the level of the patient. Similarly, the lower part of the anæsthetist's body could be protected, although it is doubtful whether it would be possible to devise suitable screening for the hands and upper part of the body. During catheterization the problem is not quite so simple. Lead rubber can be hung from the screen, but as the screen may well be moved about over the patient this may cause a measure of discomfort to the patient which cannot be tolerated for 20 minutes. Again, a protective screen over the patient's arm may well cause considerable inconvenience to the surgeon and discomfort to the patient. On the whole it is probably better to rely on personal protection in this case and reduce the risk by cutting down the screening current as far as possible and limiting the number of catheterizations carried out each week by the same surgeon so as to bring the dose to the hands within the permitted tolerance.

Summary

An account of measurements made during routine cases of angiocardiography and cardiac catheterization is given. Details of the possible doses to patient and those assisting in the treatment are computed and suggestions made as to means whereby these doses can be kept within the permitted maximum doses.

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KHELLIN IN THE TREATMENT OF ANGINA OF EFFORT

BY

H. A. DEWAR AND T. A. GRIMSON

From the Royal Victoria Infirmary, Newcastle-upon-Tyne

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Anrep, Kenawy, and Barsoum (1949) have given a historical account of the pharmacology of khellin, which is the active principle of the plant *Ammi visnaga*, from its preparation by Mustapha in 1879 and the biological studies of Samaan (1932) to their own extensive investigations, already published in various articles and now summarized and brought up to date in their latest review. They have shown that khellin, which chemically is a dimethoxy-methyl-furanochromone, is a powerful dilator of the coronary arteries of dogs and rabbits, less intense than amyl nitrite but four times as strong as aminophyllin and with the considerable merit of being prolonged in its action and, in repeated dosage, cumulative. In their clinical studies they claim that of 250 patients with angina of effort who had continuous treatment with the drug, mostly by mouth, 56 per cent showed good improvement, 34 per cent moderate benefit, and 10 per cent failed to respond. To obtain more objective results they subjected an unspecified number of patients to exercise, in order to induce pain and electrocardiographic changes, and then repeated this exercise later on the same day or on the next day, 30 minutes after an intramuscular injection of khellin, or in some cases after one or two weeks continuous treatment with the drug.

The electrocardiographic changes, RS–T depression, and T wave inversion, previously induced by the exercise are said to have been prevented when khellin was given first, and in all the patients tested the exercise tolerance is said to have improved.

The present study is concerned solely with this last aspect of the work of Anrep and his associates and an attempt has been made in a small series of carefully chosen patients, to compare khellin with glyceryl trinitrate in its capacity to prevent both anginal pain and the electrocardiographic changes that sometimes accompany it. Both drugs were given in their most active yet practical form—the glyceryl trinitrate as a tablet to be chewed in the mouth, the khellin as a liquid to be swallowed.

Method of Investigation

For convenience the investigation has been limited to male patients suffering from angina of effort. The amount of exercise required to produce moderate anginal pain was determined for each patient, and this determination repeated on each test day prior to the administration of any drug to exclude spontaneous variations in the patient's condition. By this means each patient acted as his own control, and an assessment of the relative merits of glyceryl trinitrate and khellin was obtained in all cases. In two of them a further test was made with an inert control substance. Because the patient was to be exercised several times on each of two or more days to produce anginal pain, the following criteria were adopted in the selection of cases.

(1) The patients were all men suffering from typical angina of effort.

(2) Only patients whose exercise tolerance was limited by pain were accepted. Those in whom dyspnœa was the most prominent symptom were excluded.

(3) It has long been known, and was confirmed in this investigation, that when exercise is repeated at short intervals (10–30 minutes) the amount required to cause pain may either increase

or decrease. Some, so to speak, " work it off," and in these cases, therefore, unless such increase was very slight and could be allowed for, the patient was rejected as unsuitable. When pain was provoked by decreasing amounts of exercise no allowance was necessary as the factor operated equally upon each drug used.

The decision to use exercise tolerance as a test in place of hypoxæmia was made deliberately, partly because exercise was felt to be safer and less alarming to the patient, and partly because it was undesirable to induce hypoxæmia more than once in the twenty-four hours in a patient suffering from coronary artery disease.

It was decided that the method of choice was to ask the patient to walk up and down a standard flight of stairs at a steady rate until he produced anginal pain. This form of exercise had the merits of simplicity and familiarity to the patient so that his performance was hardly likely to improve with practice. The number of trips made up and down this flight of stairs and the time taken over them were noted with a stop watch. It was found that the patients had no difficulty in maintaining a constant rate. In Cases 2 and 8 (Table I) tolerance was so limited that only exercise on the level was needed to induce pain.

Electrocardiograms were taken before and after exercise on each occasion. These provided in most cases useful objective corroboration of the development of myocardial ischæmia. In some instances, too, they showed that although one drug prevented both anginal pain and the cardiographic changes that previously accompanied it, the other drug abolished pain only, the cardiographic changes occurring as before. This allowed of a more accurate assessment of the therapeutic effect of the drug concerned.

A direct-writing Sanborn Visocardiette was used. In most patients at the first attendance leads I, II, III, aVR, aVL, aVF, and V1–6 were taken. Immediately after exercise, and while pain was still present, leads I, II, III, V1–6 were repeated. The time taken over these recordings had been reduced by practice to two minutes from the end of exercise. These tracings were studied, and the lead or leads that showed the maximum change were taken first on subsequent occasions.

In most of the patients who showed cardiographic changes these reverted to normal after the pain had ceased. Sometimes this reversion took ten to fifteen minutes, and in no case was the patient ever exercised again until the cardiogram had returned to its previous level. Since the patients used were all clear-cut cases of angina of effort, and the sole purpose of the electrocardiograms was to compare the effectiveness of drugs in preventing the temporary changes consequent on myocardial ischæmia, the single group of electrocardiographic criteria laid down by Levy *et al.* (1941) for the diagnosis of angina were not adopted, and the following graded classification of changes was used in its place.

0 =No change from the resting level, or less than that designated +.

\+ =Any of the following:
- (1) A change in the shape of the S–T segment in any lead associated with a demonstrable S–T deviation greater than 0·5 mm. but less than 1 mm.
- (2) S–T deviation of 1 mm. in any lead.
- (3) A partial inversion of the T wave or its reversal, in any lead.

++ =Any of the following:
- (1) Inversion or reversal of the T wave in any of the leads I, II, or III.
- (2) Partial inversion or reversal of T wave in any lead with S–T deviation of 1 mm.
- (3) S–T deviation greater than 1 mm., but less than 2 mm. in any lead.

+++=Any of the following:
- (1) S–T deviation in any lead of 2 mm. or more
- (2) Inversion or reversal of the T wave in any of the leads I, II, or III, with at least 1mm. S–T deviation.
- (3) Inversion or reversal of the T wave in any præcordial lead.
- (4) The appearance of a transient conduction defect.

Electrocardiograms were taken with the patients sitting in all instances except Case 5, who was recumbent on each occasion.

In all but two cases the observations were made on out-patients. As far as possible the patients attended at the same time each day, and were instructed to observe the same routine as regards time of rising, meals, method of travel to the hospital, and exercise before observation. Prior to any exercise being undertaken the patients were rested until pain had been absent for at least fifteen minutes, and the pulse rate and electrocardiogram were stable.

The two patients who were admitted to hospital (Cases 2 and 8) were suffering from severe angina of effort and nocturnal angina decubitus, and had very limited exercise tolerance. They were wheeled from their bed to the room where the observations were made, and after twenty minutes rest angina was induced by gentle exercise on the flat. The patients were tested within four days of their admission to hospital, during which time there was no improvement in their clinical condition.

Only one drug was given on any one day, and in most of the cases the drugs were tested in succession within a few days of each other. The glyceryl trinitrate mg. 0·8 (gr. 1/80) was given sublingually. The extract of *Ammi visnaga* used was kindly recommended to us by Professor Anrep. Marketed under the name of ammicardine by Alpha Laboratories, Cairo, it is an alcoholic extract standardized to contain 50 mg. of khellin per ml. Routinely the manufacturer's recommendation that the preparation be warmed in water to ensure complete solution was followed. 3 ml. (i.e. 150 mg. of khellin) were diluted in 10 ml. of tepid water. Most patients complained of a burning taste on swallowing the drug. On one occasion a patient remarked that he felt very warm after taking it. On another occasion nausea was experienced but there was no vomiting. No other untoward effects were noted. A control solution of alcohol 9 parts, infusion of quassia 1 part, was administered to two patients (Cases 2 and 5) in doses of 3 ml., diluted in 10 ml. of tepid water, to exclude the possibility that ammicardine might exert its effect by virtue of the alcoholic vehicle. Quassia was added to the alcohol to provide a bitter flavour.

Chest lead positions were outlined on the thoracic wall with a gentian violet solution to ensure that subsequent tracings would be from the same area. Care was taken to prevent the spread of electrode jelly from one præcordial lead area to another. By adopting the precautions described we have tried to eliminate most of the variable factors that occur in a therapeutic trial of this kind.

Many patients suffering from angina of effort were tested and the twelve finally used were selected for the constancy with which their pain occurred under standard conditions of exercise. This " base line " exercise was always undertaken a second time and in several cases three or four times in order not to miss the cumulative effect upon the symptom. On a subsequent day the patient returned and a preliminary control was established without drugs as outlined above. Then the patient was given one and a half tablets of glyceryl trinitrate totalling 0·81 mg. (gr. 1/80) to suck and chew. When they had totally disappeared, usually within two minutes, he was given his standardized exercise as before. Note was made as to whether pain appeared or not, and if so for how long and at the same time the appropriate electrocardiographic leads were taken. On another day exactly the same procedure was adopted except that the patient was given ammicardine 3 ml. (khellin 150 mg.) to swallow. The first few patients tested showed that when the drug acted it did so within an hour, and accordingly exercise tests with cardiographic control were always performed at 1 or 1½ hours and sometimes also at 2, 4 and 6 hours after its administration. One patient (Case 10), whose response to 3 ml. of ammicardine was disappointing, performed a further test on a separate day with 6 ml. (khellin 300 mg.).

Results

The results are given in Tables I and II. The grading of pain in the first column of Table I has been based partly on the severity but chiefly on the duration of the induced symptom, as described by the patient. In nearly all cases correlation between intensity and duration was complete, and in general it may be taken that + indicates a pain lasting less than 20 seconds, and

TABLE I

GRADES OF PAIN AFTER EXERCISE

Case No.	No drugs	After glyceryl trinitrate, 0·8 mg.	After khellin 150 mg.	Remarks
1	+ +	0	0	Age 64. Miner. Angina, moderate, for 2 yrs., associated with aortic stenosis. B.P. 140/125
2	+ + +	0	+ +	Age 44. Plumber. Angina, severe, for 6 months. B.P. 160/105. Later died from myocardial infarction
3	+ +	0	0	Age 69. Retired miner. Angina, moderate, for 2 yrs. B.P. 185/110
4	+ +	0	0	Age 66. Retired engineer. Angina, moderate, for 2½ yrs. B.P. 180/95
5	+ + +	0	0	Age 49. Priest. Angina, fairly severe, for 5 yrs. B.P. 160/100
6	+ +	0	0	Age 39. Salesman. Angina, mild, for 2 yrs. B.P. 170/110
7	+ +	0	0	Age 47. Bus conductor. Angina, mild, for 1 yr. B.P. 170/95
8	+ +	+ + +	+	Age 40. Farmer. Angina, severe, for 6 months. B.P. 130/80
9	+ + +	0	+ +	Age 48. Engineer. Angina, moderate, for 8 yrs. Myocardial infarct 7 yrs ago. B.P. 155/90
10	+ +	0	+ +	Age 45. Roadman. Angina, moderate, for 4 months. B.P. 150/90
11	+	0	+	Age 48. Miner. Angina, moderate, for 6 months. B.P. 145/90
12	+ +	+ +	0	Age 48. Miner. Angina, moderate, for 1½ years. B.P. 120/80

+++ a pain lasting more than 90 seconds. It is to be noted that these grades do not indicate the relative severity of the various patients' angina; the guiding principle was always to induce a measurable amount of pain by an exercise that did not excessively fatigue or distress him.

The results summarized in Table I show that khellin in oral doses of 150 mg. prevented anginal pain after exercise in seven cases. It permitted diminished pain in three cases, and had no effect in two. In no instance did spontaneous pain follow the administration of the drug. On two patients (Cases 5 and 8) who obtained complete relief with khellin an inert quassia alcohol mixture was without effect.

Glyceryl trinitrate in doses of 0·8 mg., prevented pain after exercise in ten cases. It had no effect on one case and on one other patient (Case 8) it actually induced pain without any exercise being undertaken. It is of interest that theophylline-ethylene diamine 0·24 g. had exactly the same effect on this man, whereas the khellin prevented pain developing after he had undertaken his

TABLE II

ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE

Case No.	No drugs	After glyceryl-trinitrate 0·8 mg.	After khellin 150 mg.
1	+ + +	0	+ + +
2	+ + +	+	+ + +
3	+ + +	+ +	+ + +
4	+ +	+	+
5	+ + +	0	0
6	+ + +	+	+ +
7	+ + +	+ + +	+ + +
8	+ +	+ + +	+
9	+ +	+	+ +
10	0	–	–
11	0	–	–
12	0	–	–

standard walk. It may be of significance that both the former drugs caused tachycardia in him, whereas khellin did not.

So far as the development of electrocardiographic change with exercise is concerned Table II shows that both glyceryl trinitrate and khellin are less effective than they are with the pain. Out of nine patients from whom satisfactory tracings were obtained, glyceryl trinitrate completely prevented the changes in two cases. It permitted decreased changes in five, but it had no effect in one, and actually induced greater changes in another (Case 8; the same patient who developed the spontaneous pain and tachycardia). On these same nine cases khellin, however, only prevented changes in one, permitted decreased changes in three, and had no effect on the tracing in five.

The changes produced by exercise in the cardiogram and the effect upon the curves of trinitrin and khellin previously administered are shown in Fig. 1, which compares the corresponding curves of the limb leads and V2 in Cases 1–4. Similar comparisons in Cases 5–7 are shown in Fig. 2 where the appearance of V4 is shown under conditions of rest, after exercise and after exercise

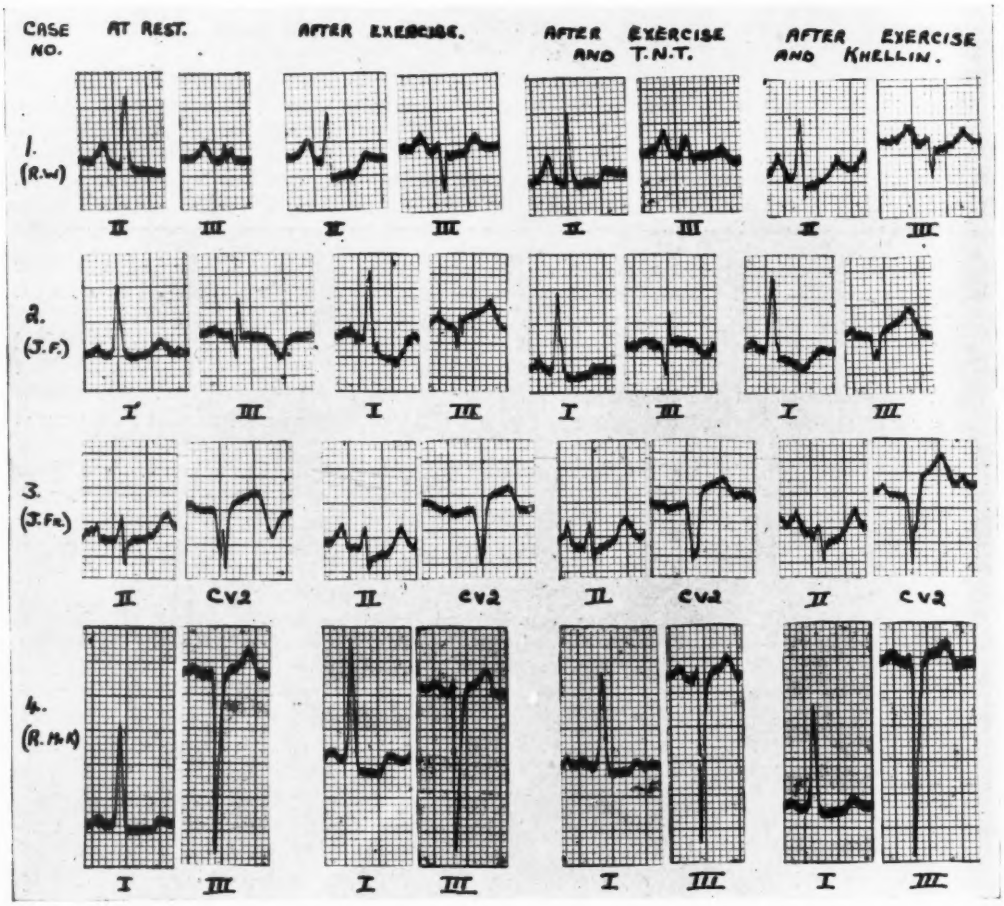

FIG. 1.—Electrocardiograms illustrating the changes induced by exercise in limb leads and lead V2, and the inflenceu of khellin and glyceryl trinitrate in modifying them.

when trinitrin and khellin had been previously given. Fig. 3 shows the record in Case 8 (referred to above); it is seen that trinitrin produces a deformity in the S–T segment in lead II comparable to that of exercise while producing a greater degree of acceleration of the heart. Exercise after the administration of khellin failed to produce any S–T deviation.

On this evidence khellin in a single dose of 150 mg. is less effective, but probably longer acting, than glyceryl trinitrate 0·8 mg. (gr. 1/80), except in the occasional patient, who, perhaps because of tachycardia, develops spontaneous pain with the latter drug. On the question as to whether a

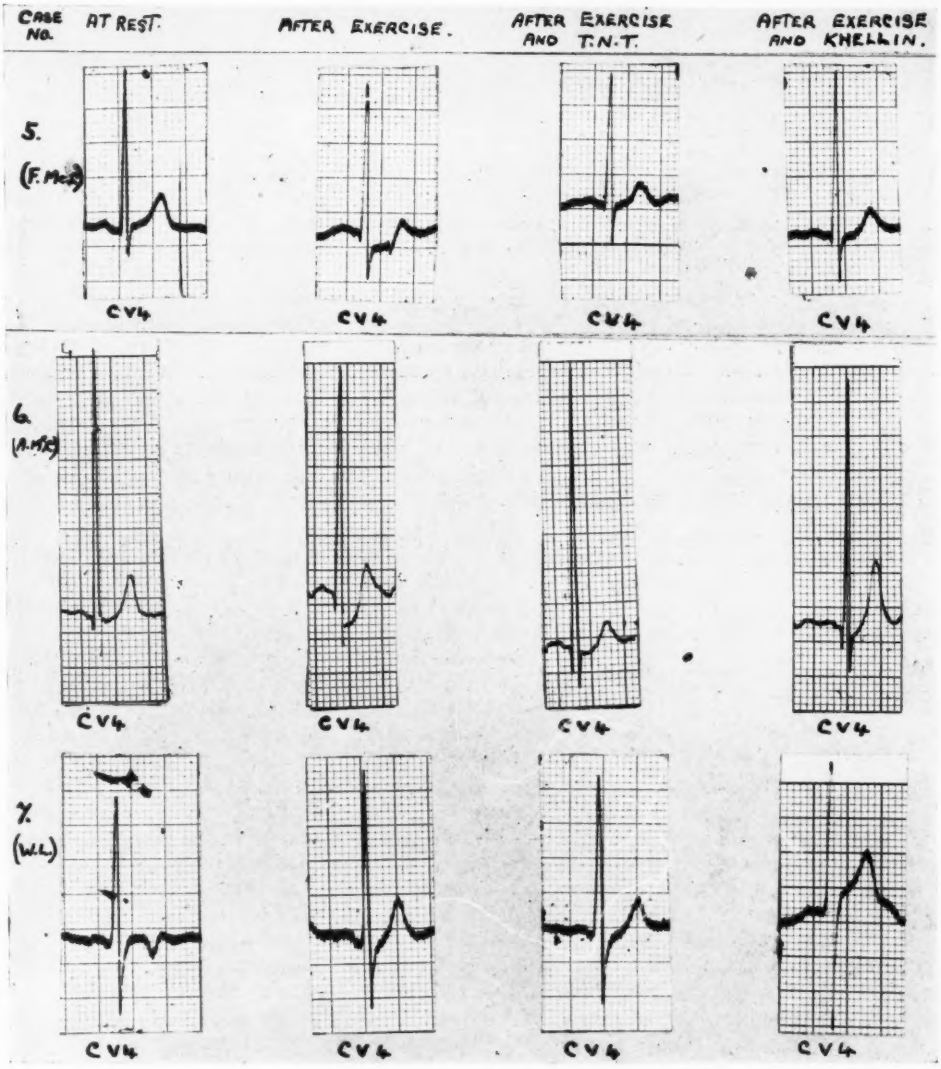

FIG. 2.—Effects of exercise and khellin and glyceryl trinitrate on lead V4.

larger dose and repeated administration would have more intense action we have no evidence. A more extended series with longer periods of observation and adequate control with inert substances will be required.

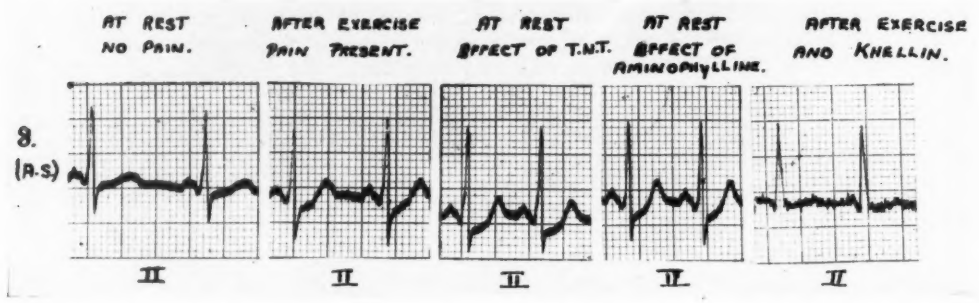

FIG. 3—Case 8. Induction of cardiographic changes by exercise. Both glyceryl trinitrate and aminophyllin induced similar changes (in association with tachycardia). Khellin allowed exercise to be taken without these changes occurring in the cardiogram.

SUMMARY

The comparative efficacy of certain doses of khellin and glyceryl trinitrate in preventing angina of effort and the electrocardiographic changes that may accompany it was tested in twelve patients.

In the doses studied, khellin is less potent but longer acting than glyceryl trinitrate.

Khellin, in doses that were effective, did not cause any unpleasant side-effects and did relieve angina in one patient who was intolerant of both glyceryl trinitrate and theophylline-ethylene-diamine.

The drug appears to warrant further study.

Our thanks are due to Professor D. Burns for facilities in his Dept. of Physiology and to the King's College Research Fund for a grant towards expenses.

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SINUS BRADYCARDIA WITH CARDIAC ASYSTOLE

BY

R. S. BRUCE PEARSON

From King's College Hospital

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A case of sinus bradycardia with cardiac asystole was described in this journal (Pearson, 1945). The subsequent history and the post-mortem findings are now recorded.

The patient was a woman aged 52 years who had been under observation since February 1943. Her pulse rate varied between 16 and 30 and her main symptoms were attacks of unconsciousness, resembling Stokes-Adams attacks; these were shown to be due to periods of asystole lasting up to 22 seconds. The shorter periods of asystole were not accompanied by loss of consciousness. At times these attacks occurred with great frequency, and on one occcasion fifteen were recorded in 45 minutes.

It was observed that exercise caused a transient increase of pulse rate; atropin 1/25 of a grain intravenously failed to increase the rate to more than 35 a minute. A radiograph of the heart and lungs at this time was entirely normal. She was discharged from hospital in August 1944.

In April 1945, the patient was seen in her home. Her condition had improved slightly and she had only once lost consciousness since January 1945. She had recorded her pulse rate daily since discharge and this varied between 26 and 33. She had been out for short walks during the previous month. Examination showed no alteration in her condition and her blood pressure was recorded as 218/140. At this time she was taking half a grain of thyroid sicca t.i.d. and half a grain of barium chloride t.i.d.

In July she began to complain of pain in the left side of her chest and was confined to bed by her own doctor. On August 8th her husband found her dead in bed. He had seen her half an hour before and at that time her condition gave no cause for anxiety, nor had she complained of feeling ill. It is presumed that she died in a syncopal attack.

Permission was obtained for an autopsy examination which showed the following findings.

The apex of the left lung was attached by recent adhesions to the chest wall and there was an effusion of moderate size at the left base. A mass could be felt at the root of the left lung spreading into the mediastinum. This proved to be a neoplasm which arose in the left upper lobe bronchus. There was very little spread into the lung itself, but a mass could be felt bounded above by the arch of the aorta and extending below to the pericardium. The heart showed some dilatation of the right auricle and ventricle. The pulmonary artery was dilated but the left main branch was considerably narrowed by the mass of growth through which it passed. There was some infiltration of the upper and posterior aspect of the parietal pericardium but the heart itself was not involved. The coronary vessels were normal. There was no evidence of atheroma of the aorta and the heart valves were also normal. The mediastinal tissues were cut by transverse incisions into four blocks about an inch thick. Neoplastic tissue invaded the mediastinum, surrounding some of the structures which normally pass through it and displacing others (Fig. 1 and 2).

I am indebted to Professor H. A. Magnus for the following report on sections of these blocks,

of the sino-auricular node, and of a portion of the left auricular wall where it was in contact with the neoplastic mass.

"Large lantern slide sections taken through the mediastinum at three different levels all show diffuse infiltration by an oat-celled bronchial carcinoma which is, in places, necrotic. The growth has completely surrounded and compressed the main vessels and numerous nerve trunks can be seen embedded in and compressed by growth.

"Sections of the left auricular wall show no evidence of growth. The area of the sino-auricular node was defined in the right auricular wall. From this area the muscle was blocked and interrupted sections were examined until the node was found. This also showed no evidence of involvement by growth." The abdominal organs were examined and no secondary deposits were found. The brain also appeared normal.

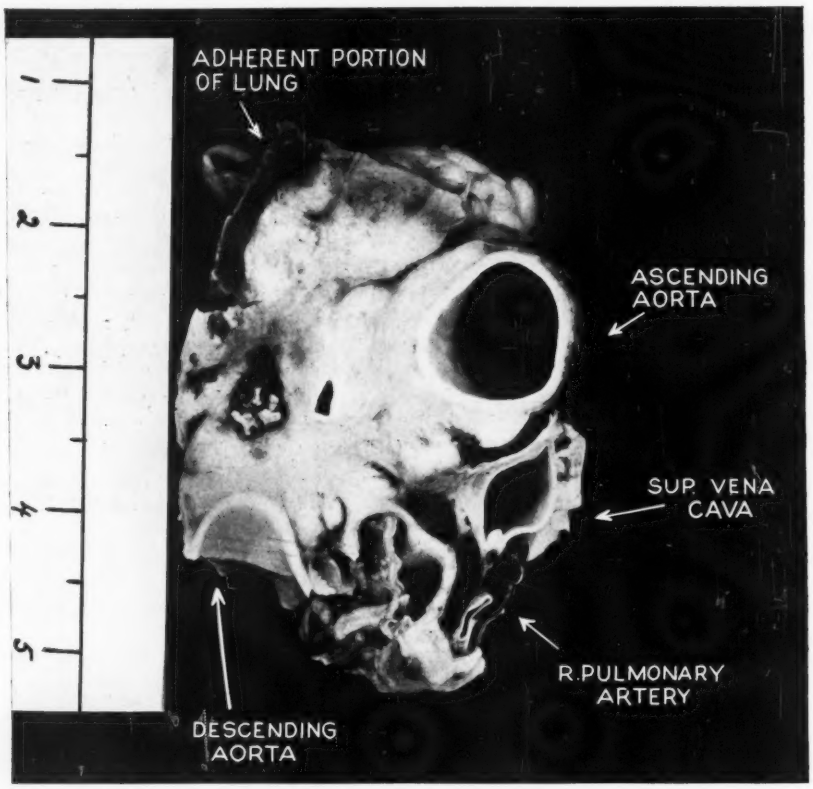

FIG. 1.—Section showing carcinoma tissue infiltrating the mediastinum, as seen from above. The constricted left branch of the pulmonary artery passes through the centre of the neoplastic mass and adjacent to it is a gland containing carbon pigment and new growth.

DISCUSSION

Unfortunately the mechanism responsible for the unique disturbances of rhythm in this case remain obscure even after autopsy. Any explanation must account for the persistent slow heart rate, the attacks of asystole, and the failure of atropin to cause a marked increase in pulse rate.

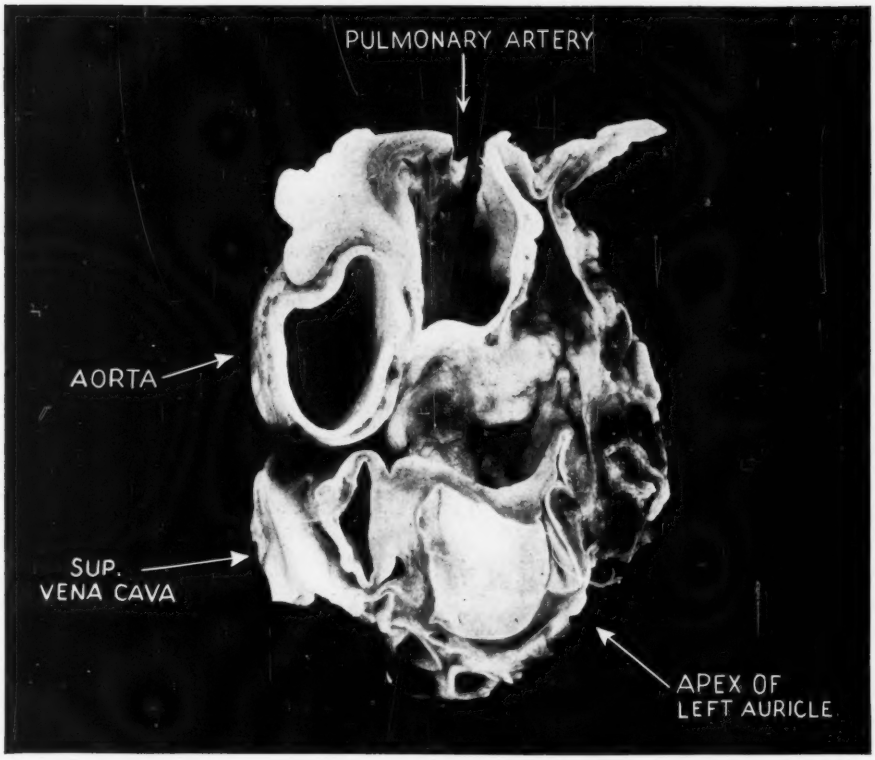

FIG. 2.—Section through the mediastinum at the base of the heart seen from below. The probe enters the dilated pulmonary artery and emerges from the branch entering the right lung. The apex of the left auricle has been cut through and the pericardial sac infiltrated with growth is seen occupying the space between it and the pulmonary artery.

There are three obvious ways by which the bronchial neoplasm might affect the heart's rhythm, (1) by infiltration of the heart muscle or specialized tissues such as the sino-auricular node, (2) by interference with the vagal or sympathetic nerves supplying the heart, or (3) by toxic effects due to the neoplasm. Finally, the association between cardiac irregularity and bronchial neoplasm in any given case may be an accidental one.

A number of articles have in recent years been written concerning cardiac arrhythmia in association with bronchial neoplasm. Twenty-eight cases have been recorded (Fishberg, 1930; Lechleitner, 1935; Auerback *et al.*, 1936; Formijne and Zuidema, 1937; Scott and Garvin, 1942; J. E. S. Pearson, 1944; Van Niewenhuizer and Kamerling, 1937).

In twenty-one, auricular fibrillation, usually paroxysmal in nature, occurred and in three of these paroxysmal flutter was also recorded; one of the remaining cases had attacks of paroxysmal flutter. Of the remaining six, one had a constant tachycardia varying between 136 and 154 (Pearson, 1944), four had simple paroxysmal tachycardia (Formijne and Zuidema, 1937; Pearson, 1944; Lechleitner, 1935, two cases), and one probably had attacks of paroxysmal ventricular tachycardia (Van Niewenhuizer and Kamerling, 1937). Post-mortem findings were recorded in twenty cases. In four only the heart and pericardium were intact, and in three the pericardium

alone was affected. The remaining thirteen showed infiltration of one or both auricles. In all these cases there was some form of tachycardia, often paroxysmal, and in the majority this could most reasonably be explained by infiltration of the heart muscle with growth. There is no resemblance between these cases and the one that forms the subject of this communication. Careful examination of the heart, including microscopy of the left auricle where it approximated to the growth, and of the sino-auricular node itself failed to reveal any evidence of direct neoplastic infiltration.

There is little doubt that many of the nerves passing to and from the cardiac plexus were subjected to considerable interference and disorganization by the neoplastic mass in the mediastinum. The superficial part of the plexus lies beneath the arch of the aorta and in front of the right pulmonary artery; it is formed by the superior cardiac branches of the left sympathetic trunk and the lower of the superior cardiac branches of the left vagus. The deep part lies in front of the bifurcation of the trachea above the point of division of the pulmonary artery and behind the aortic arch; it is supplied by sympathetic nerves from the cervical ganglion and cardiac branches of the vagus and recurrent nerves. This region between the base of the heart and the arch of the aorta was extensively infiltrated and many isolated bundles of nerve fibres were seen passing through it.

It is not easy to see how stimulation or paralysis of nerves forming the cardiac plexus could account for the changes in rhythm recorded here. Stimulation of the vagus as it passed through the growth might theoretically cause slowing and even asystole, but offers no explanation of the failure of atropin to increase the heart rate to normal. In animals it is in any case impossible to maintain vagus inhibition for any length of time and escape from vagal control constantly occurs.* Finally, it is doubtful if neoplastic infiltration can ever give rise to stimulation of nerve fibres in the neighbourhood of the growth. Complete paralysis of all vagal and sympathetic nerve fibres supplying the cardiac plexus, an unlikely possibility, would almost certainly lead to an increased heart rate and simultaneous stimulation of these nerves in animals leads to paroxysmal tachycardia and auricular fibrillation (Van Niewenhuizer).

There is no evidence in favour of toxic damage to the sino-auricular node: if this were the correct explanation, similar changes of rhythm would be expected to occur more commonly. Finally, the association between the bronchial carcinoma and the cardiac dysfunction may be coincidental. To believe that this is so still leaves the problem of the cardiac arrhythmia unsolved.

Conclusion

The autopsy findings in a case of sinus bradycardia with cardiac asystole are described. Possible explanations that might account for the disturbance of rhythm are discussed.

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ANGIOCARDIOGRAPHY IN CYANOTIC CONGENITAL HEART DISEASE

BY

MAURICE CAMPBELL AND T. H. HILLS

From the Cardiac Department and the Department of Diagnostic Radiology, Guy's Hospital

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Radiological examination of the heart has been practised from the earliest introduction of X-rays and gradually the importance of radioscopy, including the right and left oblique views, has gained ground as a valuable method of distinguishing the different chambers of the heart. In this country the method has been developed and applied largely by the teaching of Parkinson (1933 and 1936).

As early as 1931 Forssmann thought of the additional help that could be obtained in outlining the cavities of the heart after injecting opaque media by catheter. Laubry *et al.* (1935) injected hearts post-mortem and published some beautiful illustrations of the normal anatomy that found a useful basis for comparison with subsequent angiocardiograms. They showed the U-shaped right side and the window between the descending limb, formed by the right auricle, and the ascending limb, formed by the outflow tract of the right ventricle, with the right ventricle itself forming the horizontal base, and the right branch of the pulmonary artery an upper cross-bar.

In 1938 Castellanos, Pereiras, and Garcia showed some good angiocardiograms of children with congenital heart disease. They demonstrated the normal U-shaped curve of the right side, the window between the right auricle and the outflow tract of the right ventricle, and the post-stenotic dilatation of the infundibulum. Chavez *et al.* (1947) have given a summary of the gradual progress towards satisfactory angiocardiograms, referring particularly to the work of Ara, Cossio, Moniz, Carvalho and Saldanha, and Castellanos and Pereiras.

Angiocardiography was developed on a practical scale by Robb and Steinberg (1939) who published many illustrations of the additional information they obtained by this method. They found that the right auricle was shown at 1·5 sec. after the injection, the right ventricle and pulmonary artery at 2–3 sec., the pulmonary veins and left auricle at from 6 to 8 sec., and the left ventricle and aorta at from 8 to 10 sec. This work has been extended on a large scale in several centres in America.

Steinberg, Grishman, and Sussman have published a series of papers on angiocardiography in congenital heart disease, dealing particularly with a case of Fallot's tetralogy (1941), with dextrocardia (1942), with intracardiac shunts (1943*a*) with patent ductus arteriosus (1943*b*), and with the radiology of congenital heart disease (1943*c*). The paper on shunts is particularly pertinent to our present subject; 18 of the 65 congenital cases they had examined were thought to have shunts; 10 of these being through auricular defects and 2 through ventricular defects, and 6 due to an overriding aorta or one with some degree of dextro-position, 4 of these being regarded as Fallot's tetralogy and 2 as Eisenmenger's complex. Only two had post-mortem confirmation of the diagnosis.

They found the time of filling of the pulmonary vein and left auricle (3·5–4·5 sec.) and of the left ventricle and aorta (5·0–8·0 sec.) rather quicker than Robb and Steinberg, possibly because more children were examined.

The main points they used to establish auricular septal defects were those that can be demonstrated on ordinary radioscopy, but in one case they thought there was additional evidence of revisualization of the right from the left auricle after it had already emptied. Once (Case 2) they obtained evidence of a left to right shunt through the ventricular septal defect by revisualization on the right ventricle. Most of these were, of course, shunts from the left to the right side.

They found that in ventricular septal defect with an over-riding aorta (Fallot's tetralogy) there was a right to left shunt shown by simultaneous visualization of the right ventricle, pulmonary artery, aorta, and sometimes the left ventricle, within two or three seconds. Their Fig. 4 is a good example of this, and their Fig. 5 is a less convincing example of Eisenmenger's complex.

They discuss whether the injection causes a rise of pressure sufficient to reverse a left to right shunt through an auricular septal defect and mention the filling of the I.V.C. and the hepatic veins (see page 68), and think that this reversal of the shunt may have taken place in one of their cases. They mention other difficulties. (1) A slow injection (one taking 2·5 sec. or more) or blood returning from the I.V.C. may refill the right side and so simulate a left to right shunt: the amount of diodone in the S.V.C. and its movement should be watched carefully from this point of view. (2) The circulation time may be so rapid that the left side fills more quickly than usual and this may simulate a right to left shunt. (3) A large right ventricle (or auricle) may allow too much dilution for good visualization. (4) Valvular stenosis may interfere with normal filling.

Roesler (1943) in his book on radiology of the heart gives some good illustrations but does not discuss congenital heart disease in any detail. He relates the best times for getting pictures of the different chambers of the heart with the ordinary circulation times and suggests that the superior vena cava and right auricle are best seen at 1·5 sec.; the right ventricle and pulmonary artery at 1 or 2 sec. less than the arm–lung circulation time, i.e. usually about 3 sec.; and the left ventricle at 1 or 2 sec. less than the arm–tongue circulation time, i.e. generally about 6–9 sec. Sussman's *Cardiovascular System in Clinical Radiology* (1946) contains many good angiocardiograms, but does not discuss the special problems of cyanotic congenital heart disease in detail.

Chavez *et al.* (1947) produce excellent pictures of the anatomy of the heart, as the opaque substance was introduced direct into the heart through a catheter, thus enabling particular chambers to be studied in detail. They emphasize that very little of the pulmonary artery shows on the left border of the heart, though it forms the upper part of the right limb of the U; and that the right branch starts almost at a right angle to the main trunk and passes to the right; and the left branch, also going off at a right angle but passing almost directly backwards, sometimes shows as a "cap" on the top of the pulmonary artery as it turns backwards.

The left side of the heart is less pertinent to our present discussion as it is less well seen. It does not show any similar U shape form and is, in fact, rather a long oval, nearly horizontal but somewhat larger in its left side, which slopes slightly downwards, this of course, corresponding to the ventricle and the right side to the auricle. The curved upper limit of the right auricle is well shown in their Fig. 9 and 11. The question of congenital heart disease is only dealt with incidentally but their Fig. 21 shows nicely the parallel curves of the aorta and of the pulmonary artery, with a slight space or indentation, a point that showed up well in several of our congenital cases and is illustrated in our Fig. 5 and 6.

Owing to the war little was done in England until the last few years, but work is now in progress at several centres, and some preliminary results have been published (Gardner, 1948; Brocklebank, 1948; and Keele, 1948).

With the wide experience that has been gained in America it may seem unnecessary to describe our much shorter experience. The results, however, of a somewhat new method are so favourable that it may be useful to give an account of our early findings which have already proved their value all the more so as many workers are starting in this field.

In this paper we are describing the results obtained in the first 50 cyanotic cases. Since writing

it we have seen an interesting report from Donzelot *et al.* (1949) on their similar experience, five of their cases being reported in some detail.

Apparatus and Method

The apparatus has been designed by one of us (T. H. H.) and has been described elsewhere (Hills, 1948). An X-ray tube is placed at a suitable height over a special trolley, just below the top of which is a 16×16 fluorescent screen. The image produced at this plane is recorded by a large roll-film camera, and direct light from other sources is excluded from the lens by a conical box which acts as a support for the screen and maintains the correct focal distance between camera and fluorescent image.

Exposures are made at the rate of one a second on a film of such width that the finished negatives are about 5×5 in. square. Fifty consecutive exposures could be obtained, but in practice the number is normally limited to fifteen. These small films cannot at present show the detail that can be seen on a full size film, but it is easier to make comparisons between four or eight films at once and this is important in interpreting results.

In children especially, where the circulation is rapid, much will be lost if the films are not taken quickly. The time taken over the injection must vary slightly, but is generally between one and a half and two seconds. When this is about half completed a start is made so that the first film is taken in another quarter of a second, i.e. a second or a fraction more after the start. This has generally shown the right auricle filling, but nothing else, and so has given a standard of the density of the rest of the heart and great vessels without any diodone, against which the filling can be seen readily.

The interval of one second between subsequent films is accurate as it is timed mechanically.

The opaque medium used is a 70 per cent solution of diodone in water. In view of its iodine content a preliminary sensitivity test is carried out; the patient is instructed to hold a few ml. of the solution in the floor of the mouth for about one minute, and any burning or tingling sensation completely contra-indicates injection.

Successful results depend on the intravenous injection of from 40 to 50 ml. of diodone or in adults up to 70 ml. in a maximum of two seconds, and to achieve this it is usually necessary to expose a vein in the arm and inset a wide gauge canula. Donzelot *et al.* (1949) say that the injection should be " brusque mais non brutale " to avoid spasm of the veins and too much dilatation with stagnation of the diodone. A preliminary injection of 20 ml. of saline demonstrates the suitability of the vein and the speed with which the injection can be made.

The patient is told to hold his breath during the injection and to expect an extreme sensation of heat. This follows some seconds after the injection and may be very unpleasant, but reaches its maximum rapidly and fades more slowly and has usually completely passed in two minutes. There is often a brief bout of coughing and during the next few minutes there may be some nausea. A proportion of the diodone injected will remain in the vein that is selected and the gradual arrival of this further volume in the heart must be remembered or it may confuse the interpretation of the films.

It is difficult to carry out this investigation in small or nervous children without an anæsthetic. The risks of the procedure and the precautions suggested are discussed later (see pp. 69 & 70).

Direct or Oblique Views. We have used the A–P position mainly, in spite of the great value of the left oblique for many purposes. We thought that the A–P view gave fuller details of both pulmonary arteries and certainly of the systemic branches from the aorta—important information in patients who are going to have an operation. Probably it is best when pulmonary stenosis is a main part of the lesion, as in most of these cases. When relationships of the right and left ventricles are concerned, the left oblique view is certainly more valuable.

There are few cases where both views would not give useful information and this is the ideal;

but, generally, we have hesitated to give two injections, though we have sometimes done so and have no reason to think this was the cause of death of one child (see p. 69).

Rise of pressure on the right side. One important question is how much the sudden injection of this amount of fluid can raise the pressure on the right side of the heart and so cause a right to left shunt. The pressure is certainly raised because the first films often show a reversed flow into the veins of the neck or across the innominate to the other side. Even more important, there may be a reversal of flow in the inferior vena cava and hepatic veins, which means that the raised pressure had spread through the right auricle. Some reversed flow has been a noticeable feature of nearly half our cases, all of these being children, where the amount injected is relatively greater; but there were many children who did not show it.

This filling of the veins may be noticed at one, but more often at two seconds; it rarely persists beyond the third second. There may be a reflux flow to the veins of the neck (Fig. 1) or across the innominate vein to the other side (Fig. 2A). Filling of the hepatic veins is well shown in Fig. 7A and 11 and to a lesser extent in Fig. 3. In Case 0208 it persisted rather longer than usual, and this may have been of significance as she was one of two patients who died.

These changes suggest that there might be a temporary reversal of a left to right shunt through an auricular septal defect, that might lead to an incorrect diagnosis. We have, however, no particular evidence of left auricular filling in cases where there was filling of the hepatic veins. Where we have found it, there have been other reasons for thinking that there was normally a right to left shunt. We believe, therefore, that this is rarely of importance, though it is a risk of misinterpretation that needs guarding against.

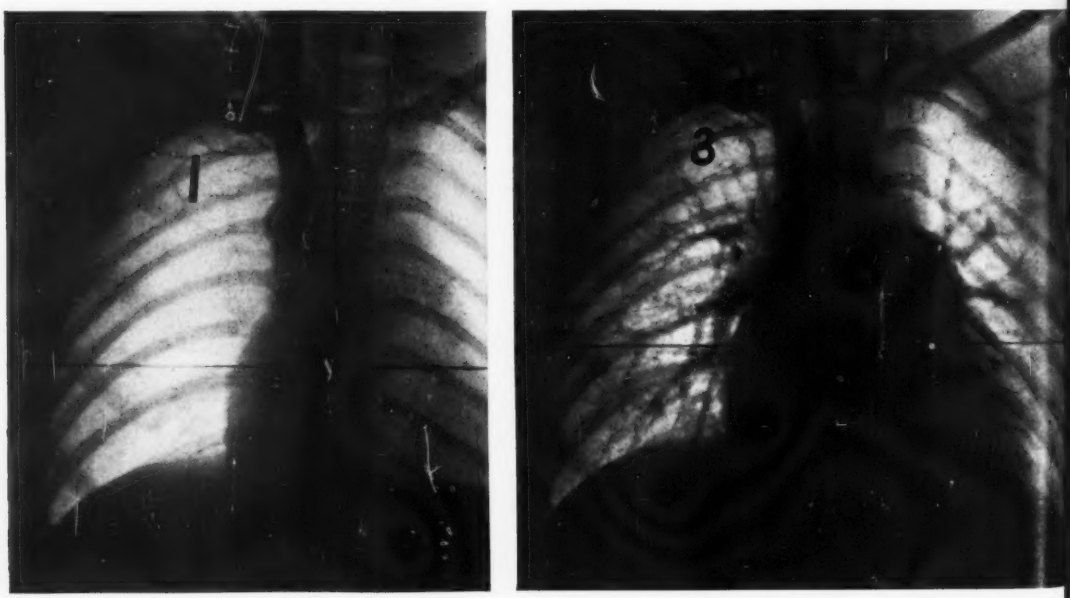


FIG. 1.—Normal filling of the pulmonary arteries for contrast with subsequent cases. It also shows reflux in the right jugular vein which has not disappeared by the third second.

(1) Diodone has filled the superior vena cava (s.v.c) and is passing into the right auricle. A good deal has flowed back into the right jugular vein and into other anastomotic veins.

(3) Right auricle, right ventricle, and pulmonary arteries are all well filled (as they were at 2 sec., but not so clearly). The main pulmonary artery is seen, dividing in the horizontal right branch and the left branch that passes backwards and is partially hidden. Smaller vessels in the lungs are already filled, with much increase in density.

It is even more difficult to think that there can be a reversal flow through a ventricular septal defect or over-riding aorta, where the difference of pressure is so much greater.

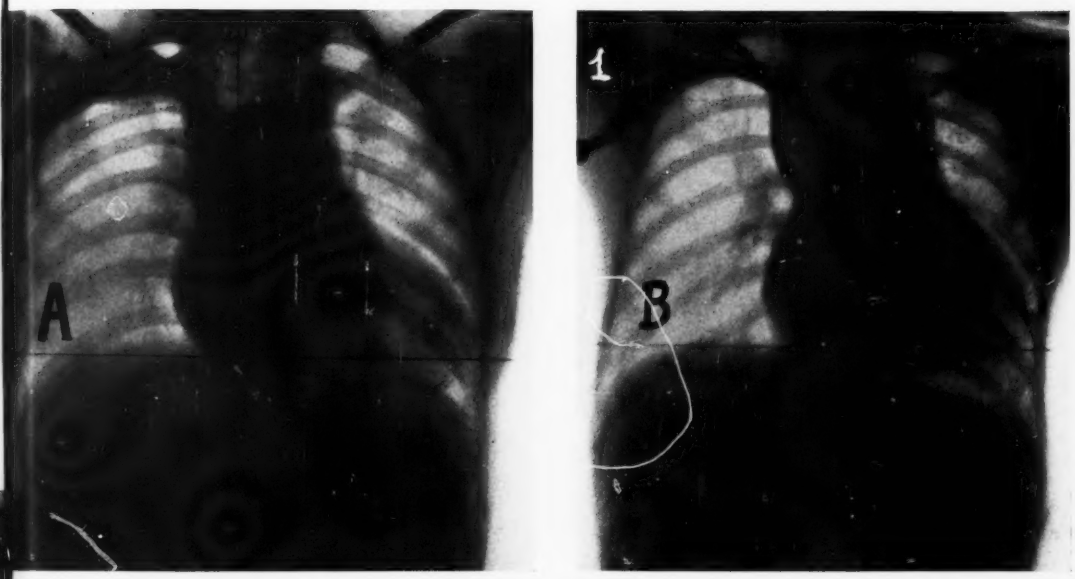


FIG. 2.—(A) Reflux filling of the innominate vein at 2 sec. Some diodone has passed into the right auricle. Fallot's tetralogy with an absence of lung filling. Case CB14.

(B) An anomalous double superior vena cava. Some dye has passed down the right s.v.c. at one sec. and can be seen lying along the outer border of the usual position of the right auricle: it tapers off and it is not certain that dye has entered the heart by this route. The main bulk has passed across to the other side and is passing downwards into the heart, possibly into the left auricle or into a common auricle. To the left of this there is a shadow that has not filled, possibly the left jugular vein entering the heart separately. The right-sided aortic arch occupies the right side of the space between. Case H126.

THE RISKS OF ANGIOCARDIOGRAPHY

Angiocardiography in cyanotic congenital heart disease is not free from risk. We had two deaths in the first thirty cases, but fortunately, there have been no other deaths in the next forty cases. Opinions have differed about the dangers of angiocardiography; we think that those who consider it free from risk have worked mainly with acyanotic and relatively fit patients, and that the risks are in the ill patients of the cyanotic group who have very little margin for any disturbance. Donzelot *et al.* (1949) appear to have had no fatalities in their cases, but think that a mortality of at least one per cent would be fully justified by the saving of life in subsequent operation and in the prevention of unnecessary thoracotomy.

A girl, aged 12, had Fallot's tetralogy with severe polycythæmia (Hb. 180 per cent). She had been in hospital some weeks with pyrexia, and bacterial endocarditis had been suspected but not confirmed. She had been allowed up and seemed in her usual health. There was no special anxiety during the procedure and she had both P–A and oblique views taken after two injections. After these were completed, though she had not recovered consciousness, her condition did not alarm the anæsthetist. On return to the ward, however, her breathing became worse and she died about fifteen minutes after the injection, despite the administration of oxygen.

On the angiocardiograms the heart seemed larger than in most cases, but this had not been so previously

and we wondered whether there was some dilatation. Nothing special was found post-mortem and there was no evidence of recent bacterial endocarditis. We felt on the whole that this was an anæsthetic death and hoped that if special precautions were taken and the oxygen continued for longer there would be no recurrence. Case CB14.

A girl, aged 14, had Fallot's tetralogy with disability and cyanosis of the highest grade and a hæmoglobin of 170 per cent, so that she was almost black and very breathless and only able to walk 10 yards. For some months she had been orthopnœic with increasingly frequent attacks of extreme cyanosis in which she was sometimes semi-conscious. The diagnosis seemed straightforward, but angiocardiography was done because it had been found increasingly useful by giving the surgeon beforehand the anatomy of the aortic branches and of the pulmonary artery. Again there were no special features to cause alarm during angiocardiography, which was done without a general anæsthetic after 2 g. of phenobarbitone given two hours before. After the X-ray had been taken she complained of the usual hot flushing in the face, headache, and nausea. These failed to disappear as they usually did in 2–3 minutes and she retched and vomited a small quantity of fluid.

For the first 10–15 minutes she appeared to be improving, but then she lost consciousness and started stertorous breathing; she appeared spastic and her cyanosis increased. Oxygen was immediately given and artificial respiration was started. After the pulse had been absent for three minutes, the cardiac impulse became impalpable and the heart sounds inaudible. Cardiac puncture then showed no movement of the needle and 5 minims of 1/1000 adrenalin were injected into the left ventricle. This started her heart beating again and artificial respiration and oxygen insufflation were continued. Despite this, and further intracardiac injection of adrenalin and nikethamide, no radial pulse ever became palpable, and after 40 minutes no cardiac action was demonstrable.

Post-mortem, the diagnosis of severe Fallot's tetralogy was confirmed, but there were no special findings to explain her death. We think angiocardiography should not have been done in such a very ill patient who had very little margin for anything. Operation would have been a great risk, but some patients as bad as this have survived with a successful result. Case 0208.

Subsequently, in view of these two deaths, we have taken at least as careful precautions before and after the general anæsthetic as for a major operation.

Anæsthetic procedure

Whatever anæsthetic is used must be given by an experienced anæsthetist with a liberal excess of oxygen. To ensure this it is better to forbid nitrous oxide completely. Cyclopropane appears to be at least as safe for these cases as anything else, and must be given in an efficiently closed system, to obviate risk of explosion.

The period of maximum danger seems to be the first fifteen minutes after the injection. The patient must be under the continuous personal supervision of the anæsthetist during the whole of this period, and oxygen must be administered by an efficient method. Sisters and nurses, however competent in dealing with ordinary cases, should not have this responsibility. The anæsthetist must personally accompany the patient back to bed, and satisfy himself that all is well before leaving him there. In most cases it is best to use an oxygen tent until full consciousness has been regained, especially when opiates have been given to control restlessness and there is, therefore, a risk of medullary depression.

Results Obtained

This paper deals with fifty consecutive cases of cyanotic heart disease where angiocardiography has been carried out at Guy's Hospital; and the results have proved of interest and of clinica value. Two acyanotic cases have been included in the section on pulmonary valvular stenosis. The patients have been grouped according to the clinical diagnosis, though occasionally this had been changed by the special investigations. Most were selected by their supposed suitability for the Blalock-Taussig operation, as we have not in general felt it justifiable to carry out this investigation where the help in diagnosis was not likely to prove of practical value to the patient.

FALLOT'S TETRALOGY

The clinical diagnosis was thought to be Fallot's tetralogy in 31 cases.

Over-riding aorta. Evidence of a right to left shunt was obtained in all these thirty-one—in one (Case 0115) only after very careful examination. In all the others this shunt was easy to demonstrate, and the aorta and its branches filled so quickly and freely (Fig. 3) that it seemed much more

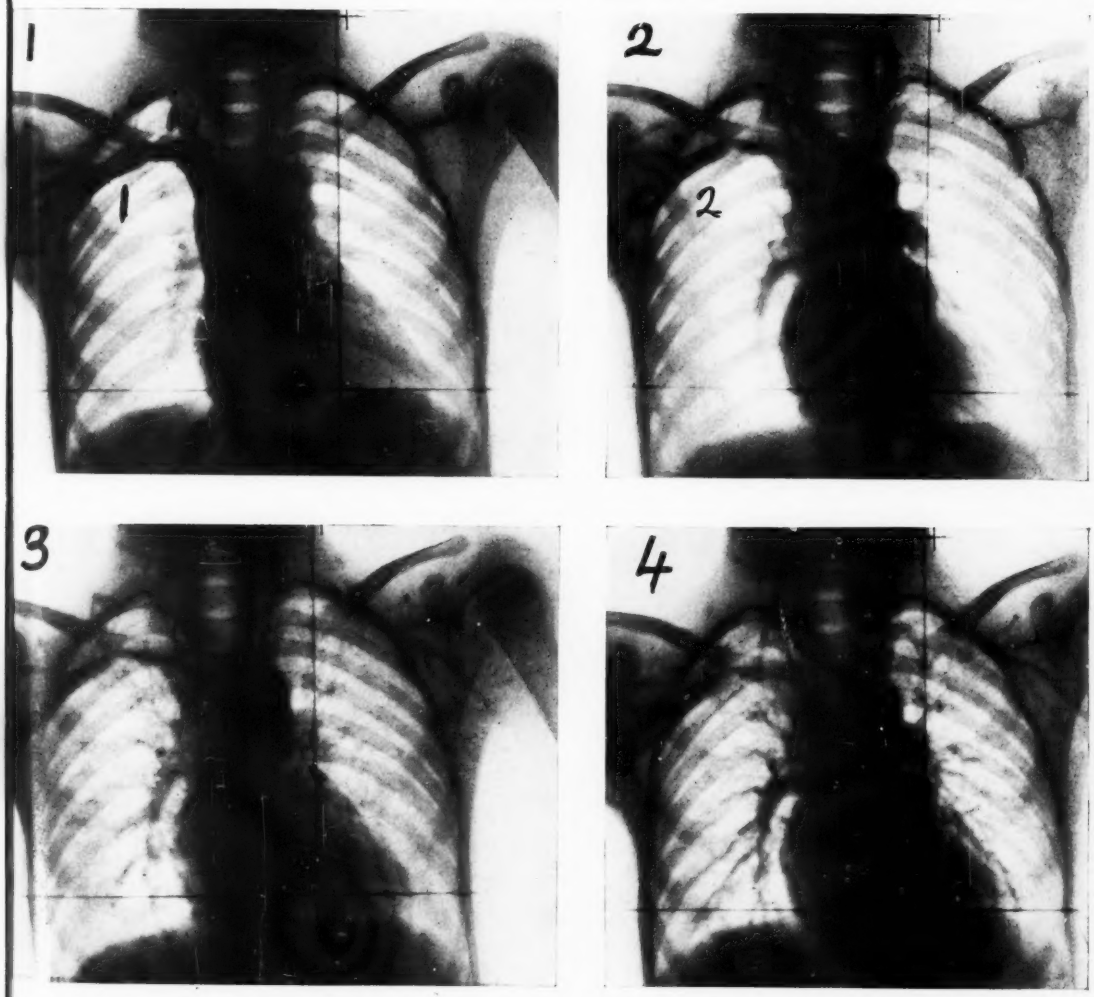


FIG. 3.—A series of angiocardiograms from a case of Fallot's tetralogy with a gross right to left shunt and moderate pulmonary stenosis.

(1) At 1 sec. the right auricle is well filled and possibly some diodone has already reached the right ventricle and aorta. Reflux into the hepatic veins can be seen.

(2) At 2 sec. the right ventricle and the aorta and its branches in the neck are much more clearly seen, and a faint shadow of the subclavian has already appeared. Both pulmonary branches can be seen, and below the left pulmonary there is a shadow that is probably a dilatation of the infundibulum above the stenosis.

(3) At 3 sec. the aorta is clearly seen, and the subclavian is better seen.

(4) At 4 sec. the aorta and subclavian are still well seen, and the lungs are now filling. Case 0053.

likely to be due to an aorta that over-rode the right ventricle than to one that filled entirely from the left ventricle with the right to left shunt through a septal defect, quite apart from the direct observation in many cases that the left ventricle showed no signs of having filled.

Generally, the right to left shunt was described as large (18 cases) or moderate (12 cases); only in the one already referred to was it described as slight and then could not be seen till 4 seconds. As a rule the aorta was well filled at 2 seconds (20 cases) but sometimes not till 3 seconds (10 cases). The amount seen in the aorta and its branches seemed a better guide than whether the aorta could first be seen clearly at 2 or at 3 seconds.

At first, we were impressed by the ease with which filling could be seen in the abdominal aorta and the renal artery, but later, because of the importance of the anatomy of the neck vessels, have taken films at a higher level, so that the innominate, carotid, and subclavian have been the branches most noted. The filling of the subclavian on the side *opposite* to that used for the injection is of particular value and is often well seen at the third and fourth or even the second second (Fig. 4).

We have little experience of similar angiocardiograms in normal subjects for comparison; a subclavian that is filling in the normal way after circulation through the lungs cannot generally

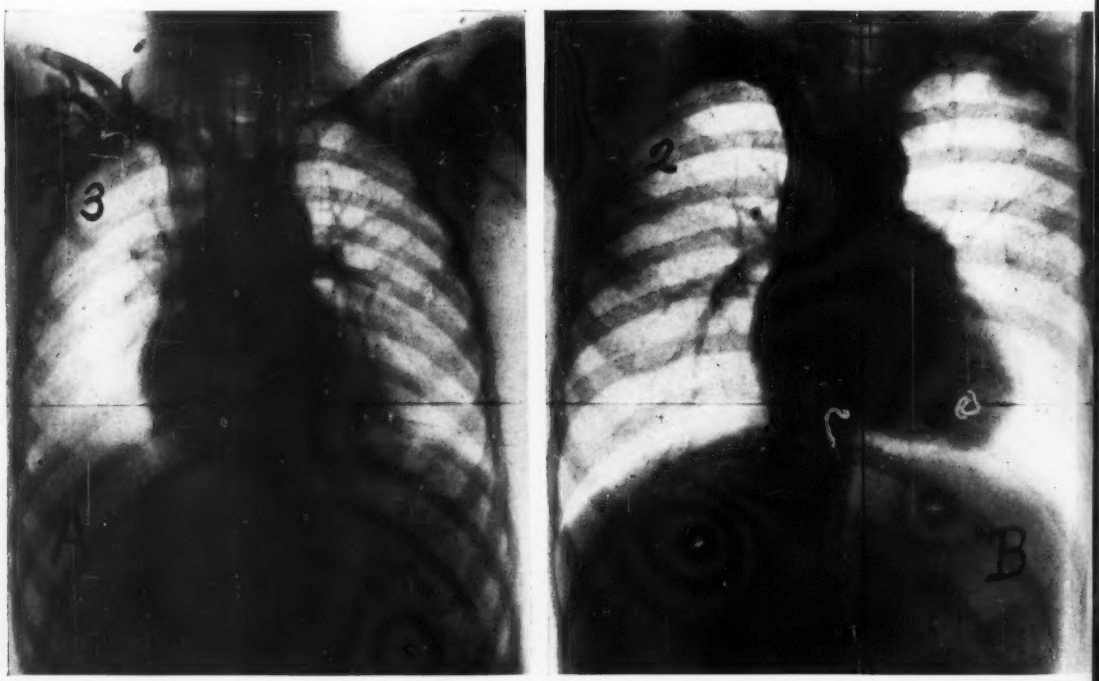


FIG. 4.—Angiocardiograms from two typical cases of Fallot's tetralogy.

(A) The right auricle and ventricle are both seen at 3 sec., but the main feature is the over-riding aorta, so uncoiled that the ascending arch and descending part can easily be seen, and also well below the diaphragm. The innominate, carotid, and subclavian arteries are well shown, and probably the vertebral arteries, but there is little detail about the infundibular region or pulmonary arteries, though that on the left is seen. Case P046.

(B) The right auricle, right ventricle and the aorta and its branches are shown at 2 sec. The left subclavian is seen less clearly, and probably the left internal mammary artery. The dilatation of the infundibulum beyond the stenosis is clearly seen below the left-sided aorta. The right pulmonary artery is visible, but the left is hidden posteriorly. The contrast between the uncoiled aorta in (A) and the vertically placed aorta in (B) is striking. Case 0107.

be seen until 6 or 7 seconds, even in children; though Dr. Frances Gardner informs us that she has found it happening within 4 seconds in a small child.

In straightforward examples where the clinical diagnosis of rather severe Fallot's tetralogy was confirmed by other methods, the results of angiocardiography seemed clear and decisive. Typical reports were as follows.

The right auricle fills at a normal rate. Dye is seen in the aorta at three, and in the right renal artery at six seconds. The pulmonary arteries are never well filled and show maximum concentration at five seconds. There is a considerable volume shunt from right to left and a major degree of pulmonary stenosis. Case 0105.

The right auricle is well outlined at two seconds. At three seconds dye is seen in the pulmonary arteries, and the aortic arch, and is already filling the left subclavian artery. The lung fields show little increase in density throughout the series. A considerable right to left shunt and marked pulmonary stenosis. Case 0185.

The dye outlines a normal right auricle. There is a large right to left shunt outlining an over-riding aorta two seconds after the end of the injection. The pulmonary arteries are best filled at four seconds, but the concentration is poor. Case CB09.

The second of these is shown in Fig. 5B and the aorta, pulmonary artery, and dilated infundibulum can be well seen, forming the three main features going downwards. Fig 5A shows what

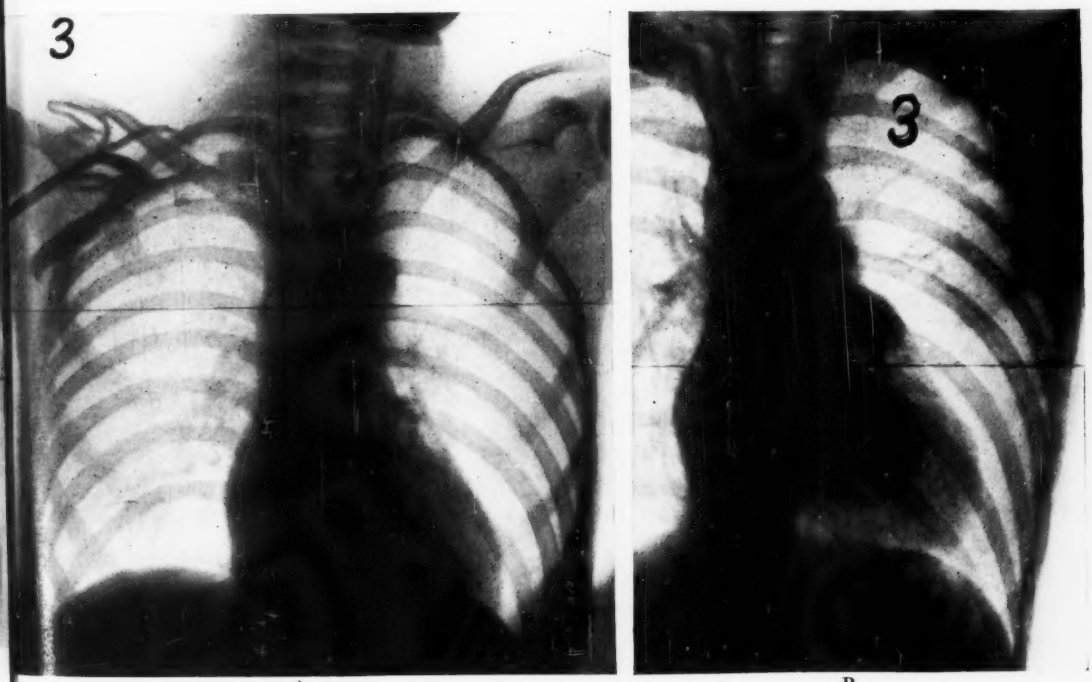


FIG. 5.—Angiocardiograms at 3 sec. in two contrasted types of Fallot's tetralogy. The right auricle and right ventricle are filled in both.

(A) represents what we have called the " dull " picture because the high grade pulmonary stenosis prevents much marking in the lungs, and there is little to see except the quickly filled over-riding aorta and its branches. Case 0208.

(B) shows a more interesting picture, where the infundibular dilatation beyond the stenosis can be seen below the left pulmonary branch, which is itself below the aortic knuckle. These three, with the lighter outline of the left ventricle, form four distinct arcs on the left border of the heart. Case 0185.

we have called the " dull " picture of Fallot's tetralogy where the high grade stenosis prevents any real increase in the pulmonary arterial shadows, and there is only the over-riding aorta. This variety is much more common than would be thought on the illustrations chosen, as owing to their close resemblance few have been reproduced.

Pulmonary stenosis. Angiocardiography seemed less decisive or at least more difficult as regards the diagnosis of pulmonary stenosis. In Fallot's tetralogy the outflow tract of the right ventricle is of very variable shape, as can be seen from the figures. In some cases one sees nothing more than the border of the right ventricle and the pulmonary artery itself, and has to judge the stenosis solely by the degree of filling of the lungs (Fig. 5A). In others, a rounded shadow may be seen that appears to be the dilated infundibulum distal to the stenosis (Fig. 5B).

In these 31 cases this shadow could be seen easily in 12 (Fig. 3, 4B, 6, 7, and 8) with less certainty in 6, and could not be recognized in 13 (Fig. 2A and 5A). Sometimes this same shadow can be seen on the straight X-ray though then, of course, it is not so certain what it is. Fig. 7 gives a good example of two rounded shadows one of which could be seen on the straight X-ray while the other could not.

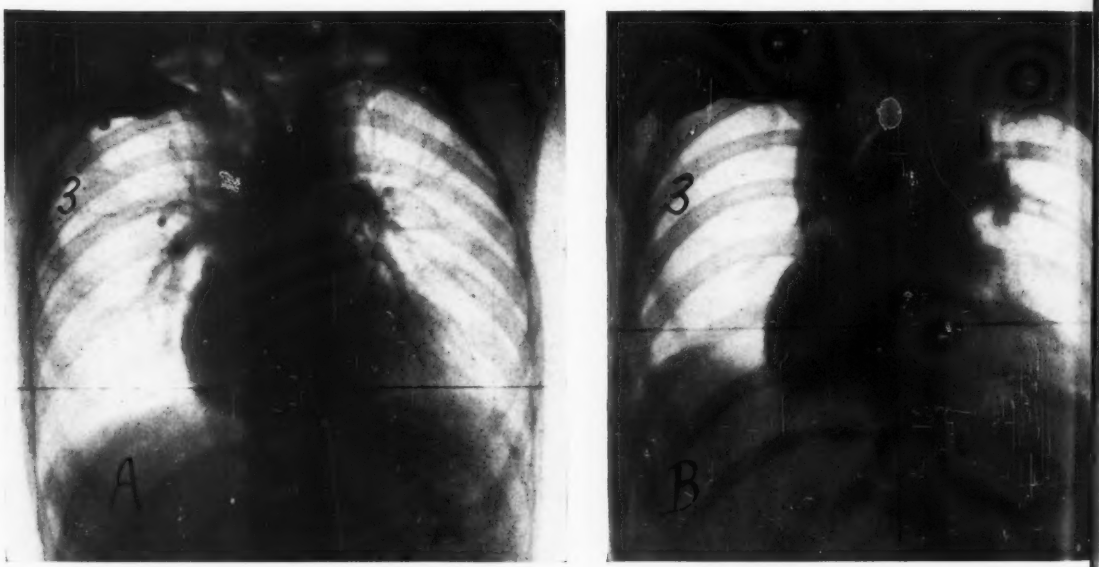


FIG. 6.—Two cases of Fallot's tetralogy, where the aorta is wide and the arch horizontal, with the left pulmonary branch forming a second arch below this. Although the pulmonary artery is well seen there is little filling of the lungs. Both are taken at 3 sec.

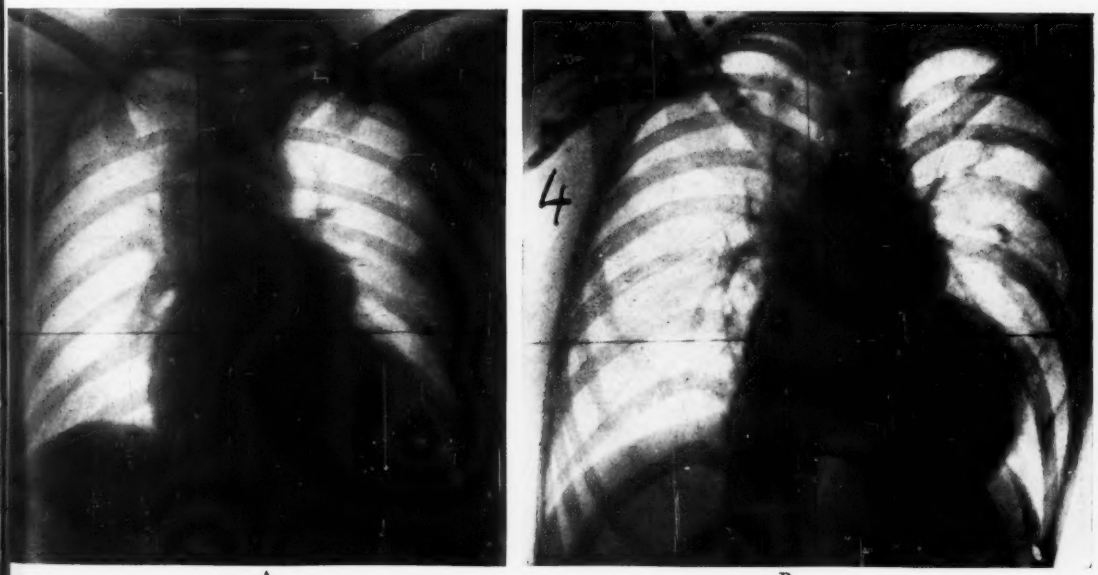
(A) Dilatation of the infundibulum beyond the stenosis which passes directly to the right pulmonary branch, with the left pulmonary branch going off at an acute angle and lying just below the aortic arch. Case 0089.

(B) The right ventricle seems denser than the right auricle, and the left ventricle is not filled. The shadow above the stenosis is well seen, but this infundibular dilatation in contrast with (A) seems to pass more directly to the left pulmonary branch and the right is hardly seen. Case CB12.

We have estimated the degree of stenosis by the amount of filling of the pulmonary arteries and of the lungs, apart from this evidence of a dilatation beyond the stenosis. The mere fact of the pulmonary arteries filling at two seconds at the same time as the aorta is no evidence against pulmonary stenosis. If there is much pulmonary blood flow there will be a steady increase in the density of the lung fields and this would appear to be a better guide than the condition of the main pulmonary arteries, though these, too, are of some value.

The estimate of the degree of pulmonary stenosis was made entirely by one of us (T. H.) who at the time was unaware of the clinical diagnosis, so that it was based entirely on the angiocardiograms. Finally, the degree of pulmonary stenosis was arbitrarily classified, again by T. H., into six grades, five suggesting almost pulmonary atresia, and one little or no pulmonary stenosis.

The 31 cases in this group were classified as follows—grade 4 or above, eight; grade 3, nine; grade 2, eight; and lower grades than this, six cases. Of the six who died four had grade 3 pulmonary stenosis or more, and two had grade 2 stenosis only. Even in these two it was considerable, as the infundibular stenosis diameter measured between 3 and 4 mm. only in one and was described as slit-like in the other (Fig. 8).



A B

FIG. 7.—Two cases of Fallot's tetralogy with considerable dilatation of the infundibulum.

(A) The aorta is less well seen than in many cases at 3 sec., suggesting that there may be a smaller right to left shunt than usual. The infundibular dilatation could be seen on a straight X-ray, but its nature was less certain. There is extreme pulmonary stenosis. Case CB11.

(B) The over-riding aorta is well seen at 4 sec., and the rounded shadow which includes the dilated infundibulum and pulmonary artery fills the hollow below the arch. It could not be recognized easily on a straight X-ray, perhaps because of the severe scoliosis. Case 0080.

We do not feel satisfied that the degree of pulmonary stenosis can be assessed in this way. There were 16 cases where cardiac catheterization allowed a calculation of the pulmonary blood flow, though this too, is only an estimate. In eight of these with grade 4 or 5 pulmonary stenosis, catheterization suggested an average pulmonary flow of 44 per cent of normal; in six with grade 2–3 pulmonary stenosis, 50 per cent of normal, and in two with grade 1 or 2 pulmonary stenosis 57 per cent of normal. Considering the wide range of the individual figures these average differences are not very significant. In one patient where hesitation was felt about operation because the pulmonary stenosis was thought to be so slight, the relatively high figure of 70 per cent of a normal pulmonary blood flow was found.

Of the 25 cases with pulmonary stenosis classed as grade 2 or above, 18 have already had a successful operation and only one had a completed operation that produced relatively little improvement, probably because of surgical difficulties (P056).

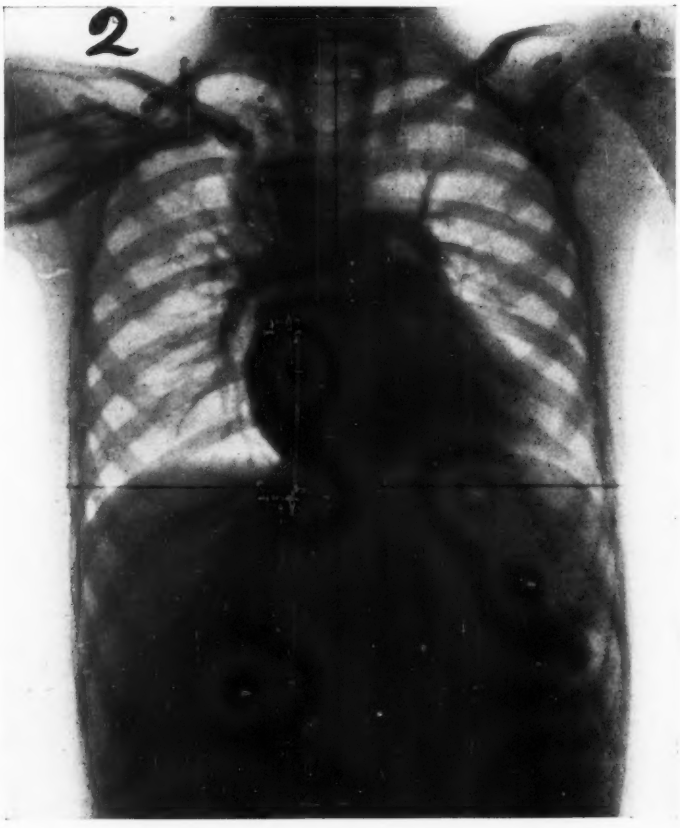


FIG. 8.—Fallot's tetralogy, showing dilatation of the infundibulum beyond the stenosis. The diagnosis was confirmed post-mortem. At 2 sec. the right auricle and ventricle are well filled, and a right-sided aortic arch. There is considerable dilatation beyond the infundibular stenosis, and both pulmonary branches are well seen, but the lungs do not fill much. Retrograde filling of the hepatic veins is well shown. Case P023.

Cases with less evidence of pulmonary stenosis. There remain the 6 cases where the degree of pulmonary stenosis was thought to be less than usual, between grades 1 and 2 (4 cases) and between 0 and 1 (2 cases). It is interesting as showing our growing reliance on angiocardiography that two of these cases occurred early and no hesitation was felt about operating. The other four were seen later and it was only after much thought and further observation of the patients that it was decided to operate. We were encouraged in this by the great improvement in the two former patients, both in their capacity for exertion and in their colour.

The two cases where there seemed least evidence of pulmonary stenosis are described in more detail.

A girl, aged 8, was moderately cyanosed, but had attacks of deep cyanosis in which she went semi-conscious. These were getting worse, so that walking along the ward might provoke an attack, sometimes with complete loss of consciousness. Cardiac catheterization showed increased pressure, 80/10 mm. Hg. in the right ventricle, but the pulmonary artery was not entered. Angiocardiography showed a high degree of over-riding aorta (Fig. 9). This was the first case where refilling of the subclavian artery was observed

after the dye had been through the lungs; and as this occurred at six or seven seconds, it was felt that there was no significant pulmonary stenosis. Operation was decided on after much hesitation, but so far (six months) she appears greatly improved. Case 0042.

A boy, of 18, had moderate cyanosis from birth, and severe disability. Clinically, he seemed a typical example of Fallot's tetralogy. On screening the lung fields were more dense than usual, but we thought that the lungs were oligæmic and that he was suitable for operation. On angiocardiography he was at first thought to have no pulmonary stenosis, but finally a very slight degree. He was, therefore, an excellent test case for the value of operation in this group and other patients were delayed pending the result of his operation.

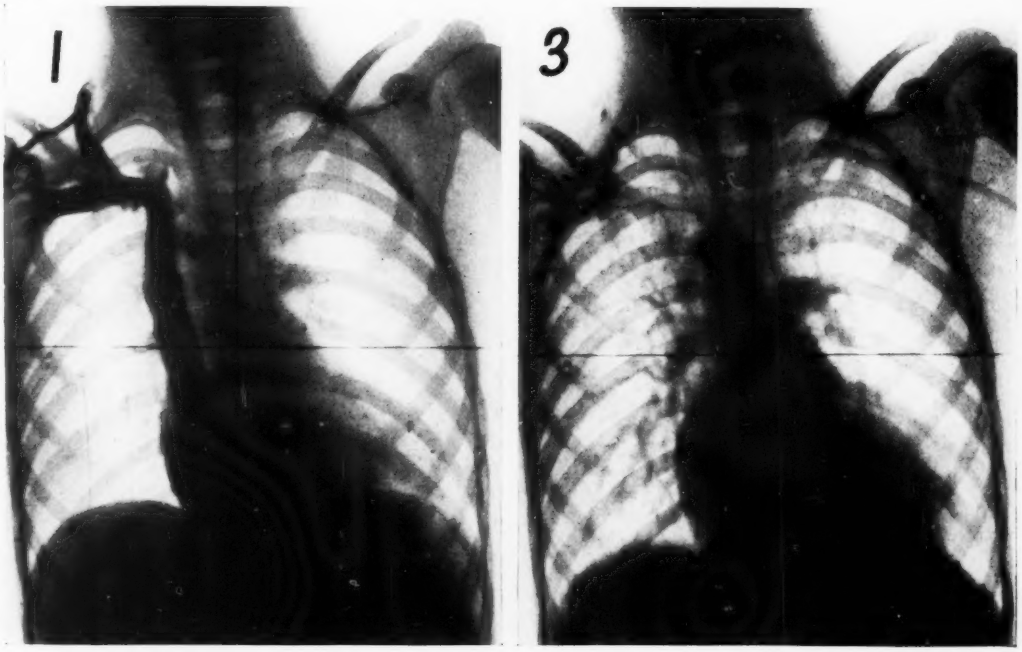


FIG. 9.—Fallot's tetralogy with a gross right to left shunt and minimal pulmonary stenosis.
(1) At 1 sec. the right auricle is filled, and the right ventricle to a slight extent.
(3) At 3 sec. the heart is better filled. The right-sided aorta is easily seen, and its branches, and the left-subclavian, specially clearly, indicating an over-riding aorta, which was already well seen at 2 sec. The pulmonary arteries are also well filled, and the lung fields, as a whole, are filling.
The subclavian artery, which had completely disappeared by 5 and 6 sec. showed up again at 7 sec. with blood that had circulated through the lungs. Case 0042.

Ten weeks after, the result was extremely good. He was at school and getting about normally all day. He had already walked a mile with ease compared with the 200 yards that he had been able to walk previously. His colour was almost normal except for slight cyanosis in the nails. On screening, both pulmonary arteries were seen more easily than in most cases after operation, and pulsation could now be seen in both branches. There was, however, no congestion of the lungs and no undue increase in the size of the heart. His progress was equally good after eight months. Case 0067.

In these two cases the pulmonary stenosis was probably much less than usual, and the disability more due to the over-riding aorta taking the bulk of the blood. In general, the operation seems to have produced as much improvement in those thought to have slighter grades of pulmonary stenosis. This at first sight is rather surprising. It may be that our estimate of the relative degrees

of stenosis is not correct, but we think it indicates that a subclavian-pulmonary anastomosis is helpful for the abnormality produced by the over-riding aorta, re-directing to the lungs some of the blood that should have gone there direct, though, possibly with a greater risk of susbequent cardiac enlargement from the increased work.

Except in six cases where the pulmonary infundibular stenosis was confirmed after death, there is of course, no absolute proof of its presence, but the other evidence supports it.

Case Somewhat Resembling Fallot's Tetralogy

A girl, aged 7, was thought to have Fallot's tetralogy, but was unusual in the absence of a systolic murmur and in some increased density of the lung roots, which it was thought might be due to collateral vessels. (Case P048.)

On angiocardiography there was early filling of the left ventricle and the aorta filled before the pulmonary arteries. The lightness of the lung fields supported pulmonary stenosis, though the right lung filling better than the left suggested a right-sided patent ductus. There was no clinical evidence of this and we should have suspected large bronchial arteries. There seemed to be atresia of the left pulmonary artery, but radioscopy suggested that there might be a vessel here that would be adequate for an anastomosis.

The interpretation of the angiocardiogram was correct in this particular, and at operation the left pulmonary artery seemed atresic and no anastomosis could be performed. After her death the findings were still difficult. The blood supply to the lungs was through dilated bronchial arteries; at first, she was thought to have a common arterial trunk, but finally an atresic pulmonary artery was found.*

Fallot's Tetralogy or Pulmonary Atresia with Patent Ductus or Bronchial Arteries

There were five patients where the clinical picture of Fallot's tetralogy was associated with signs suggesting a patent ductus arteriosus. These cases will be given very shortly as others have been investigated since and raise problems that can be discussed best on a larger number. A continuous murmur may be produced by enlarged bronchial arteries, and lungs filling in this way may often be recognized. The cases fall into four groups, Fallot's tetralogy or pulmonary atresia both with a patent ductus, or pulmonary atresia or a common arterial trunk, both with enlarged bronchial arteries. It is difficult to distinguish the last two conditions.

One of these (Case 0021) is being fully reported as post-mortem there was pulmonary atresia with the blood supply to the lungs through a patent ductus (Allanby, Brinton, Campbell and Gardner, 1950). Although it was not recognized at first, as the right to left shunt was thought to be through a ventricular septal defect, she was a good example of an auricular septal defect with the rather horizontal curve of the upper border of the left auricle showing clearly (Fig. 10).

A second (Case P021) had signs of patent ductus on the right (with a right-sided arch) and much more blood flow to the right lung than to the left, with a dilated pulmonary artery on the right side. This was obvious on ordinary X-rays and more so on angiocardiography. An over-riding right-sided aorta filled at 2 seconds. There was so little filling of the left lung (Fig. 11) that operation was performed on this side with some anxiety as to whether any pulmonary artery suitable for anastomosis would be found. Fortunately, in spite of the poor filling, the artery was of reasonable size, though thin-walled, and a good anastomosis could be carried out. Pulmonary atresia cannot be excluded, but the pulmonary root shadows were not nodular and the left pulmonary artery found at operation also seemed rather against this.

The third (Case 0087) seemed much the same clinically, except that the ductus murmur was on the left and the lung filling seemed to be nodular rather than through a normal pulmonary artery. It was hoped that he had Fallot's tetralogy with a patent ductus, though the exaggerated sabot-

* Now that the necropsy findings are known it would be easy to present this case in a simpler form. We have, however, felt in this and other instances that the difficulties and mistakes that have arisen will be useful, and have left the picture as it appeared clinically.

shaped heart with the deep pulmonary bay and the nodular filling suggest pulmonary atresia. On angiocardiography the aorta filled at 3 seconds, showing a gross right to left shunt. The arch was high and left-sided, but there was an additional vessel on the right, a large innominate or possibly a remnant of a partial right-sided arch. The pulmonary shadows did not show any filling till 4 seconds and the upper right lung became denser than the left, with no evidence of normal right or left main pulmonary arteries (Fig. 12).

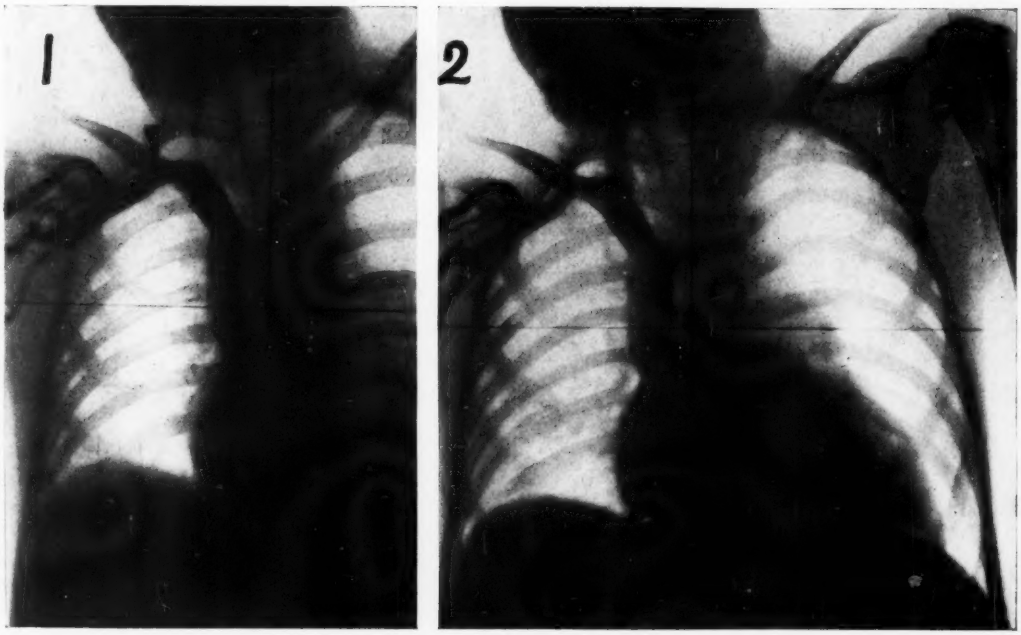


FIG. 10.—Filling of the left auricle in pulmonary atresia with a closed ventricular septum.
(1) At 1 sec. the right auricle is filled.
(2) At 2 sec. the diodone has passed over to the left, and the almost horizontal curved upper border is typical of filling of the left auricle. The aorta cannot yet be seen. Case 0021.

At operation conditions seemed very abnormal and no pulmonary artery to which an anastomosis could be made was found. There appeared to be a vessel arising from the upper side of the subclavian or innominate and coursing downward into the lung; looking back at the films, this could be made out. We think now that this nodular appearance where the left pulmonary artery should be, with filling of the lung high up on the right side means an absence of the main pulmonary trunk, the lungs getting their blood supply from the aorta through bronchial arteries.* The final diagnosis is pulmonary atresia or possibly a common arterial trunk (though the narrowness of the shadow is against this) with the lungs filling from the bronchial arteries.

The fourth (Case 0191) was similar clinically and on angiocardiography, but the evidence was less clear and she was not submitted to operation.

The fifth (Case 0181) need not be discussed, as clinical examination, catheterization, and angiocardiography (made more difficult by her being 25 years of age and overweight) have failed to produce reasonable certainty about the diagnosis.

* Frances Gardner has independently emphasized these two features as characteristic of hypertrophied bronchial arteries and we have borrowed the word " nodular " from her description. A series of such cases is being reported (Campbell and Gardner, 1950).

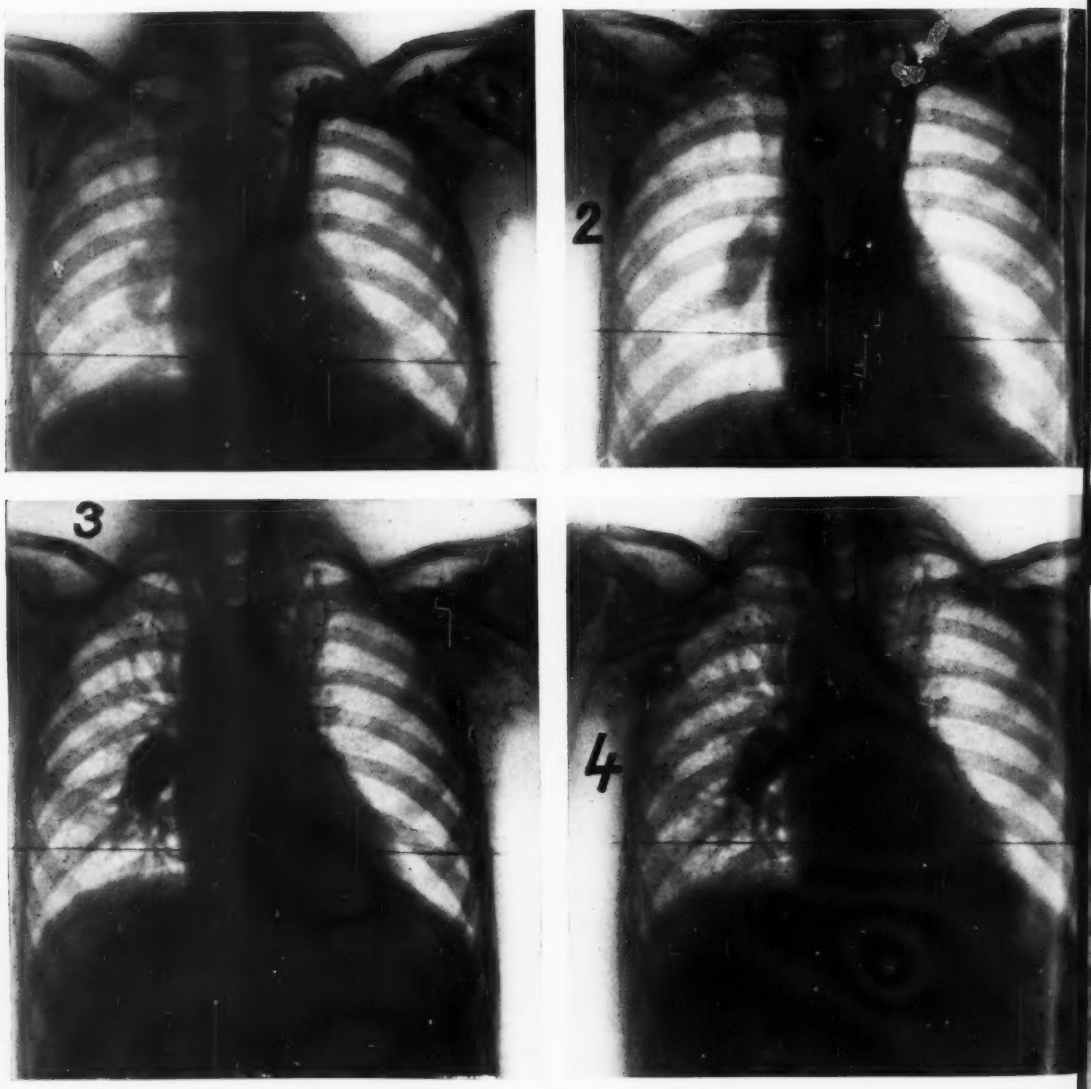


FIG. 11.—Fallot's tetralogy with a right-sided patent ductus arteriosus.

(1) At 1 sec. the *left-sided* s.v.c. is well seen, filling the left side of the right auricle. A fine trickle passes across the innominate vein to the right side, and catheterization had shown that there was also a s.v.c. on the right.

(2) At 2 sec. the right auricle, right ventricle, and right-sided aorta and its branches are filled. The dilated right pulmonary has filled a little, but probably through the patent ductus, as it does not seem to connect with the main shadow of the heart.

(3) At 3 sec. the same features can be seen in the heart which is now more obscured, and also the subclavian and some reflux to the hepatic veins. The dilated right P.A. is now much fuller and the right lung is becoming dense, but there is very little filling of the left lung.

(4) At 4 sec. the aorta and dilated P.A. are less dense, though there is more general filling of the right lung. The subclavian is still well seen. Case P021.

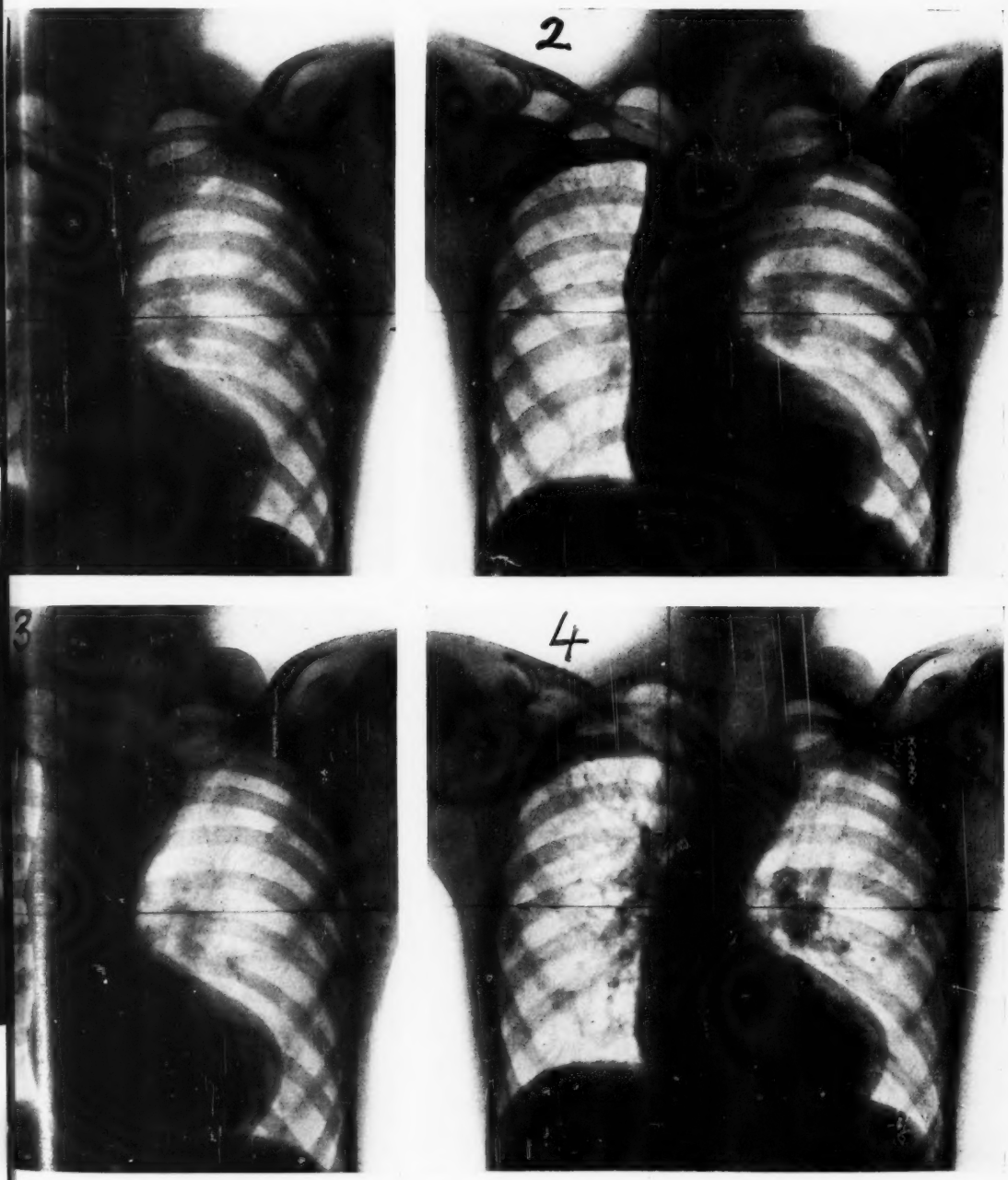


FIG. 12.—Angiocardiograms from a case of pulmonary atresia with filling of the lungs through bronchial arteries.

(1) At 1 sec., little seen except the filling of the s.v.c.

(2) At 2 sec. the diodone has passed down the rather narrowed s.v.c. to the right auricle and ventricle, and the lower part of the aorta is filling.

(3) At 3 sec. the aorta is seen much better (and the subclavian) and there is a wide branch to the right as well as the left-sided aortic arch. There is very little filling of the lungs.

(4) At 4 sec. the aorta is still well seen and the subclavian and the branch to the right are more dense. The lungs are now filling, but there is no trace of main pulmonary arteries, the right lung filling higher up and rather diffusely and the left lung filling in two or three isolated areas, where presumably there is dilatation of the bronchial arteries around the lung root. Case 0087.

Of the 37 patients so far considered all had a right to left shunt. In Case 0021 with pulmonary atresia, the shunt was through an auricular septal defect—a type that will be seen again in the next group of tricuspid atresia, and in a modified form through a patent foramen ovale in the group that follows with pulmonary valvular stenosis.

In the other 36 cases the right to left shunt was thought to be through an over-riding aorta, presumably with a high ventricular septal defect, though some of the three just discussed (Cases 0087, 0181, and 0191) may have had a common arterial trunk.

Tricuspid Atresia

The other patients not diagnosed clinically as Fallot's tetralogy, were rather varied, but several were of interest and the angiogram was often helpful in confirming or suggesting a diagnosis. Two had tricuspid atresia with a non-functioning right ventricle. This diagnosis was made on a general clinical picture like Fallot's tetralogy, but with left instead of right axis deviation in the electrocardiogram and left rather than right ventricular hypertrophy on radioscopy (Brown, 1936).

In the first (Case P057), the report of T. H. who, as usual, at the time he wrote it, had not been told the clinical diagnosis, was as follows.

> The right auricle is small and the dye is seen entering the left ventricle at two seconds. At three seconds the right-sided aortic arch and the great vessels in the neck are opacified; at four seconds the abdominal aorta, and at six seconds the left renal artery are seen.
>
> The pulmonary arteries are never well shown and begin to opacify at four seconds, and on the subsequent films the region of the right ventricle becomes a little denser.
>
> There is a major shunt from right to left. The right ventricle filling after the left suggests that the only significant communication with this chamber is from the left ventricle.

Blood reaching the left ventricle from the right auricle without filling the right ventricle must pass through a defect of the auricular septum. Re-examination of the films shows that this is so and the upper border of the left auricle can be seen outlined at 2 seconds (Fig. 14).

This rather horizontal curve is characteristic of the upper outline of the left auricle and should

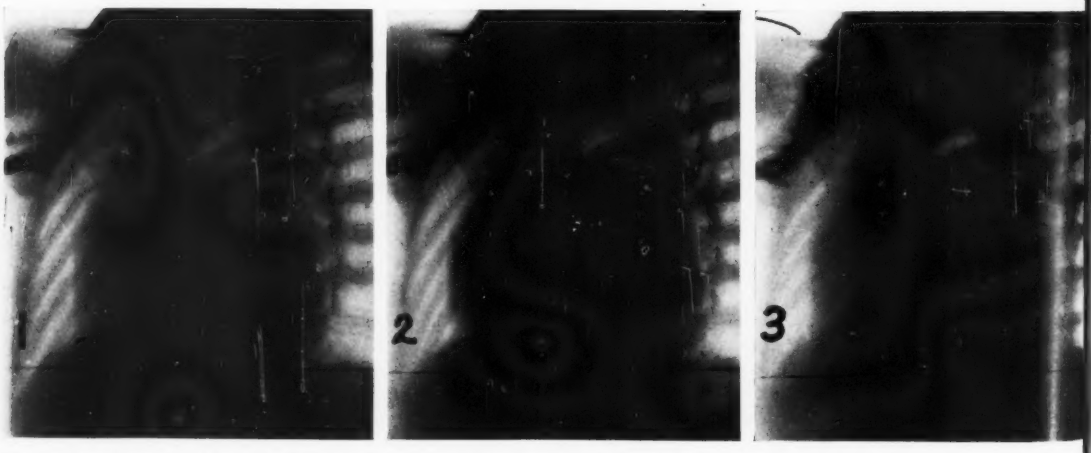


Fig. 13.—Left oblique angiocardiograms showing filling of the left auricle in tricuspid atresia.
(1) At 1 sec. most of the diodone is still in the s.v.c.
(2) At 2 sec. the right and left auricles have become dense. Looking back, after examining (3) the aorta and pulmonary artery can be seen faintly.
(3) At 3 sec. the right side of the heart is fading though the left auricle and ventricle are still dense; the aorta and the pulmonary arches are well seen passing backwards. Case 0007.

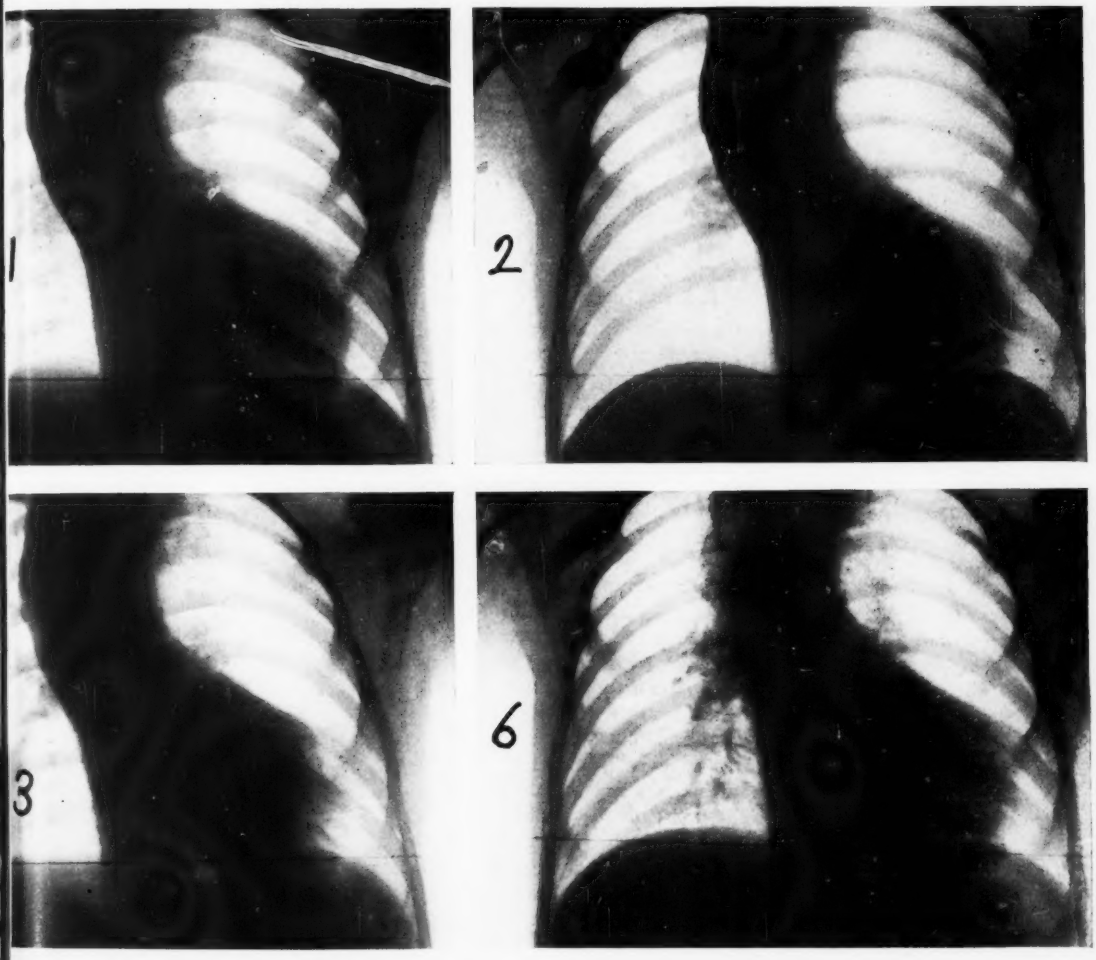


FIG. 14.—Filling of the left auricle in tricuspid atresia.
(1) At 1 sec. some diodone has reached the right auricle and passed across to the left auricle.
(2) At 2 sec. the left auricle and left ventricle are more clearly seen and a faint right-sided aortic arch is indenting the s.v.c. The triangular hollow between the spine, the diaphragm and the left ventricle, indicates an absence of any significant right ventricle.
(3) At 3 sec. the outlines are denser, especially of the aorta.
(6) At 6 sec. the same shadows can be seen, but less clearly. The subclavian has filled and the lungs are beginning to fill through the pulmonary arteries. The right ventricular window is present but fainter. Case P057.

always be looked for when a right to left shunt through the auricular septum is suspected. The clear space low down in the mid-line—which we suggest calling the right ventricular window—shows up well. It became less obvious from 6 seconds onwards as the right ventricle gradually filled from the left ventricle (Fig. 14).

In the second (Case 0007) the findings were very similar, the horizontal upper border of the left auricle being well seen at 3 seconds in the P.A. (not shown, as similar to Fig. 10) and even better in the left (II) oblique view, and the aorta in the same film, (Fig. 13), though presumably a trifle

later. It was less obvious that the left ventricle was filled, but the translucency in the region of the right ventricle supports the view that it was the left ventricle.

The catheter could not be passed into a right ventricle in either of these cases: nor was it, in fact, passed through the auricular septal defect into the left auricle, which is more surprising. In Case 0007 the arterial blood was not much more saturated (59%) than that in the right auricle (53%) which might be expected, as probably the pulmonary flow was very small. In Case P057 the difference was greater (73% against 56%).

Both patients benefited from a subclavian-pulmonary anastomosis, but not perhaps as much as most patients with Fallot's tetralogy, though the former has been able to leave his home and go to a government training centre for watch making.

Pure Pulmonary Valvular Stenosis

One of the commoner cyanotic conditions after—but a long way after—Fallot's tetralogy is pulmonary valvular stenosis. There were six cases where this was found and in four this was confirmed, post-mortem. Details of the clinical picture and pathological anatomy have been reported by Allanby and Campbell (1949).

Four were cyanosed, and evidence of a right to left shunt was found by angiocardiography, though at first in one it was thought to be due to an over-riding aorta and in another it was missed and was not recognized till the subclavian artery was seen to be filled at 5 seconds. A fifth was cyanosed, and we think that he has a right to left shunt, but can see no evidence of it. The sixth was acyanotic, and there was no reason to suspect a shunt.

Sometimes in this group the shunt needs looking for more carefully than in Fallot's tetralogy. The aorta and its branches are seen so much less easily because the diodone reaches the left side much more slowly and sometimes in smaller quantity through the small patency of the foramen ovale. An over-riding aorta provides an easy direct route to the aorta and systemic arteries and is seen quickly and easily.

The evidence for a right to left shunt through the patent foramen ovale was less easily seen than in tricuspid atresia where *all* the blood was flowing through an auricular septal defect.

In this group there was thought to be a very high degree of stenosis (grade 5, two cases; grade 4–5, three, and grade 4, one case), preventing much blood flow to the lungs. This and the relatively small shunt through the foramen ovale and the absence of an over-riding aorta to carry away the diodone quickly mean that the heart empties slowly and that after the first two or three seconds subsequent films show very slow changes. This comment was made on the first report of nearly all these cases before we had realized its full significance—" little change from 6 to 12 sec.", " little change from 3 to 10 sec.", and " heart still contains much dye at 14 sec.", and might have warned us against the diagnosis of an over-riding aorta in the case where this was wrongly suspected (Case 0041).

D. S. (Case H117) was first thought to have Fallot's tetralogy, but questioning her mother afterwards revealed that the history of cyanosis from birth was wrong, and that after being blue *at* birth no change of colour was noticed again until she was 18, after which she became progressively and severely blue, and noticed clubbing of the fingers from 25 till her death at 29. The angiocardiographic report was a major pulmonary stenosis with no shunt: the circulation times and

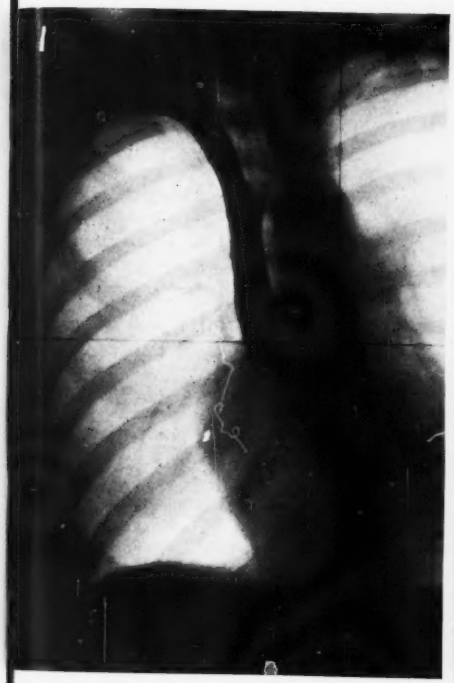
FIG. 15.—Pulmonary valvular stenosis with patent foramen ovale.

(1) At 1 sec. diodone is entering the right auricle.

(3) At 3 sec. the right auricle is well filled and the left auricle and perhaps the aorta slightly; the las confirmed by the left subclavian being visible at 4 sec.

(6) At 6 sec. there is not much change, but more filling of the left ventricle and a little of the left monary artery. The delay in emptying the right auricle and ventricle confirms obstruction without any outlet such as an over-riding aorta.

(10) At 10 sec. there is still a good deal in the heart, but very little in the lungs, though the pulmo branches can be seen better now and the density in the heart is rather less. The subclavian artery is still seen. Case H117.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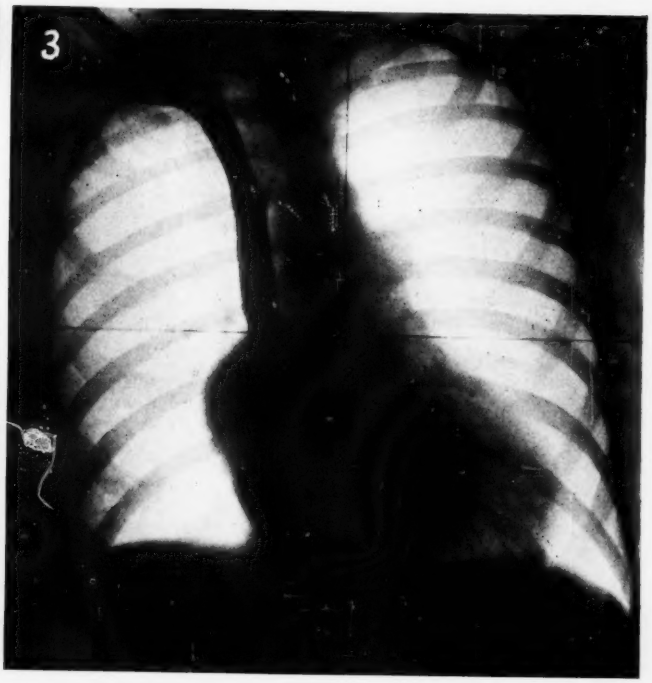
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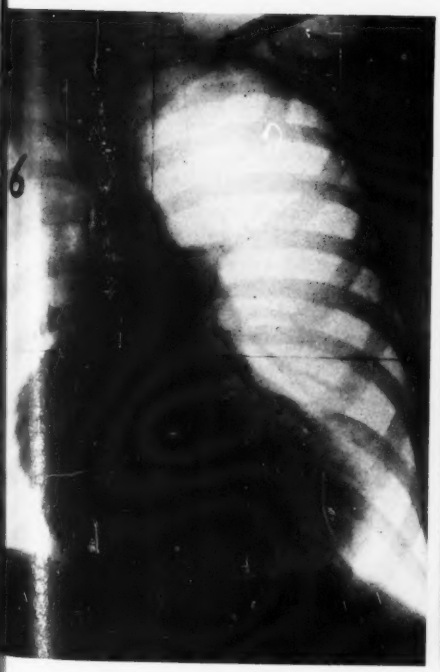
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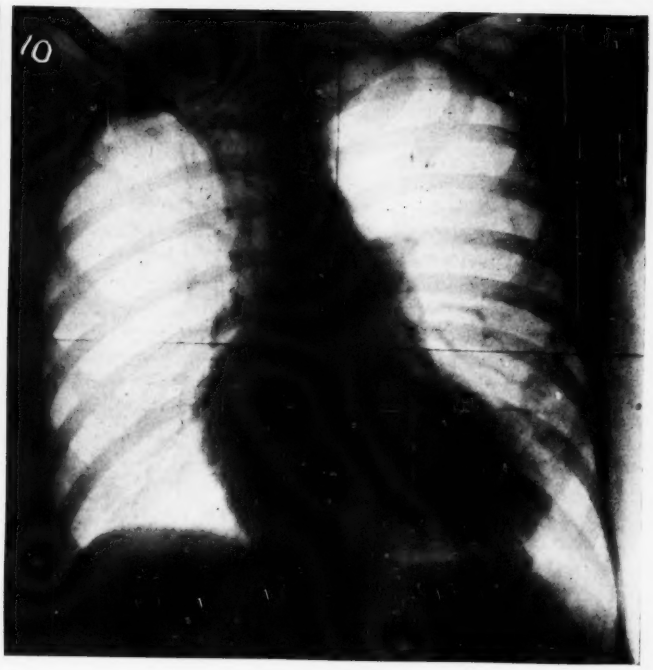
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cardiac catheterization both showed much delay in the circulation and suggested high grade stenosis with only a small right to left shunt. When she died there was severe pulmonary valvular stenosis (diameter 3 mm.) and a slit-like patent foramen ovale, 7×3 mm., partially covered by the usual valve flap.

Re-examination of the angiocardiograms showed the aorta was lightly visible at 3 and 4 seconds and the left subclavian at 5 and 6 seconds (Fig. 15), so that as in others where the aorta was not over-riding it filled more slowly because of the time taken to pass through the septal defect and the left auricle and ventricle. A faint shadow indicated the filling of the left auricle from the right auricle, but the left ventricle was poorly filled, perhaps because of ventricular systole.

R. P. (Case 0124) was similar, except that the right to left shunt was recognized at once. The right auricle was not well opacified till 4 seconds, when some diodone could already be seen out to the edge of the left ventricle. The aorta and the pulmonary arteries were both seen at 6 seconds. Here too, the diagnosis was confirmed post-mortem, and as the foramen ovale admitted the tip of one finger, filling of the left side might have been expected earlier. On the angiocardiogram alone it was not possible to say that the shunt was through a defect in the auricular septum, but this could probably have been shown in the left (II) oblique position.

G. B. (Case 0041) had the main features of Fallot's tetralogy, but cyanosis was not noticed till she was four, and she did not squat. On screening she showed a very prominent pulmonary artery and some apparent enlargement of the left ventricle as well as of the right, though the latter was greater: on these findings the provisional diagnosis was Eisenmenger's complex.

A year later the heart was larger (c.t.r. 63 instead of 57) and the prominence of the pulmonary artery certainly no less; we thought, with increasing experience of this type that she had pulmonary valvular stenosis with a dilated pulmonary artery, and a large patent foramen ovale, for the cyanosis was gross.

Angiocardiography showed extreme pulmonary stenosis and apparently an over-riding aorta, but did not look like Fallot's tetralogy in that the heart as a whole was still dense at 8 seconds, which should have made us more doubtful about an over-riding aorta that would have taken away the diodone more quickly (Fig. 16). No evidence of the right to left shunt through an auricular septal defect, as with other similar cases, was seen.

Cardiac catheterization showed very low oxygen saturation, and very high pressure in the right ventricle; the pulmonary artery was not entered. The diagnosis was pulmonary valvular stenosis with a patent foramen ovale, but it remained somewhat doubtful, as Fallot's tetralogy with a high grade of pulmonary valvular stenosis seemed an alternative.

At operation, valvular stenosis was confirmed, but the heart stopped before this could be relieved. Post-mortem, the righ to left shunt was through a patent foramen ovale.

The fourth (Case P076) is still alive, so the diagnosis is not proved. There had been cyanosis from birth without much polycythæmia or clubbing of the fingers, and right bundle branch block was thought to favour auricular septal defect and radioscopy favoured pulmonary stenosis. The angiocardiogram suggested a major pulmonary stenosis and a moderate right to left shunt, probably through a patent foramen ovale; there was little change in the shadows from 3 to 10 sec. Catheterization supported these findings.

In the other two cases there was no evidence of a right to left shunt. The first (Case OA11) provided a good example of the normal U-shaped filling of the heart and poor filling of the lungs, thus supporting the diagnosis of pulmonary valvular stenosis with no evidence of a shunt. We cannot think that this diagnosis was correct, as he had been cyanosed from nine months old, and increasingly so. Cardiac catheterization supported the view that he had pulmonary stenosis and also a right to left shunt.

The second (Case P212) had a very large right auricle (and indeed a very large heart), and the filling showed the normal U-shaped curve of the right side of the heart (Fig. 17). The pulmonary stenosis was thought to be of the highest grade (the diameter of the pulmonary orifice was 3 mm., post-mortem), and the aorta and its branches were not visualized. She had a very large pulsating liver and a diagnosis of tricuspid regurgitation was made. There was a fan-shaped shadow passing from the angle of the auricle and the inferior vena cava out into the liver which was, we think,

produced by tricuspid regurgitation, but it can hardly be seen in Fig. 17. All these points made in the diagnosis were confirmed post-mortem.

These last two cases are the first good demonstration of the normal U-shaped filling of the right side of the heart, because in most cases of Fallot's tetralogy the C-shaped over-riding aorta quickly fills in the hollow of the U, and when the opaque substance passes from the right to the left auricle this also obscures the hollow.

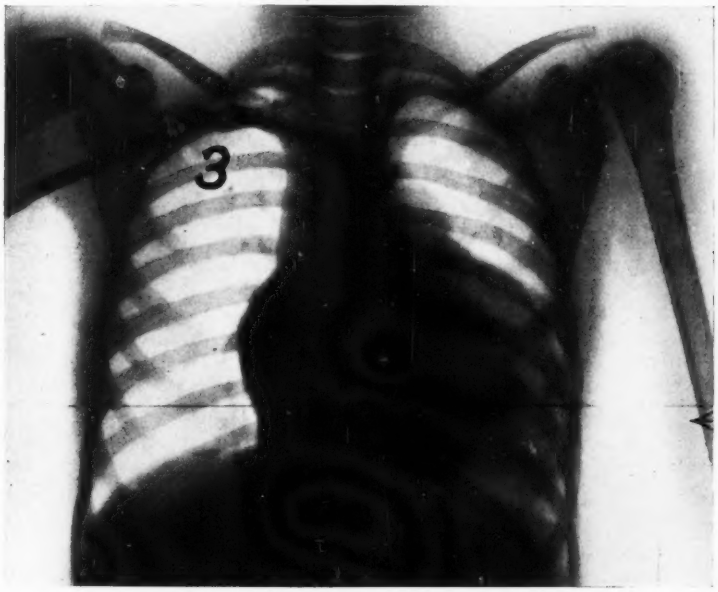


FIG. 16.—Pulmonary valvular stenosis with patent foramen ovale.
At 3 sec. a large right auricle and the right ventricle are well seen, but no pulmonary artery. The aorta and its branches have filled well—in fact, from the left ventricle and left auricle, though there was difficulty in excluding an over-riding aorta; the general delay in the emptying of the heart was one of the main arguments against this. Case 0041.

A seventh patient (Case 0368) was originally included in this group as the physical signs and the absence of cyanosis suggested the diagnosis of pure pulmonary stenosis. The original report of the angiocardiogram suggested moderate pulmonary stenosis, and that the aorta opacified faintly at three and more at four seconds, indicating a moderate right to left shunt or over-riding aorta.

It seemed doubtful if this could be correct as normal circulation times supported the clinical view of no significant right to left shunt. When a final analysis showed he was the only case where a shunt had been found without clinical cyanosis, further re-examination of the films showed that there was no evidence of a shunt, the change in the aorta being doubtful and nothing being certain till the subclavian artery filled at 7 and 8 seconds, which might have been normal filling through the lungs as the pulmonary stenosis was not severe. Probably, the mistake arose from accepting an aorta that could just be seen for one that had become opacified but apart from anything else this should not have happened, because of its distance from the left border of the superior vena cava, which is generally indented by the aorta and shows where the latter will be before it becomes opaque. We mention this mistake because in any doubtful aorta the filling of the branches should always be looked for.

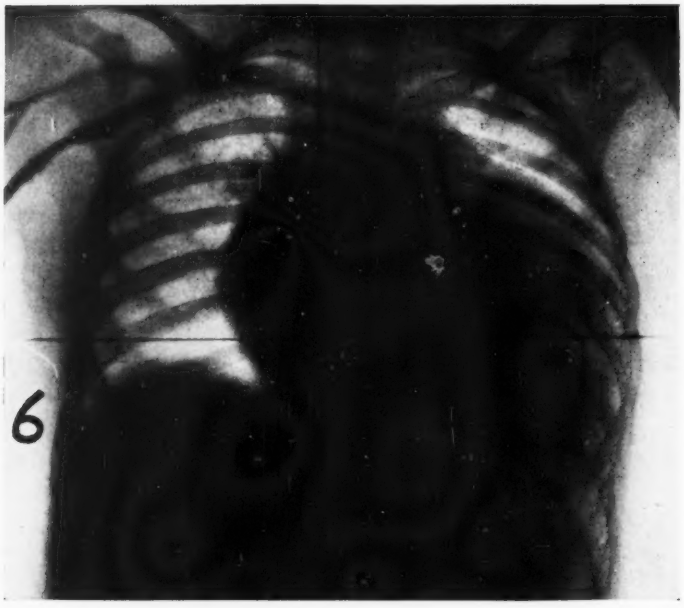


FIG. 17.—Pulmonary valvular stenosis with closed septa.

A large right auricle and large right ventricle were filled, without any signs of a right to left shunt or significant filling of the lungs at 2 sec. (not shown).

At 6 sec. the U-shape of the right side of the heart can be seen with the densest shadow at the upper part of the left limb of the U showing the dilated pulmonary artery above the valvular stenosis. There is still very little filling of the lungs and no signs of any right to left shunt. The film at 12 sec. (not shown) still showed a good deal of diodone on the right side and the pulmonary artery a little more filled, but the aorta was not visible. Case P212.

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY

Two cases with this clinical diagnosis are included. Angiocardiography suggested the transposition was complete in one and not so complete in the other.

The former, Case 0052, was 9 years old and was only able to walk a few yards. He had been moderately cyanosed from birth, with gross clubbing of the fingers and polycythæmia, the hæmoglobin being 148 per cent. Triple rhythm combined with a loud but variable booming second sound in the pulmonary area were the most noticeable physical signs.

Radioscopy showed a slight increase in the size of the heart, mainly of the right ventricle, but a great increase in both pulmonary arteries and their branches, which could be easily seen spreading through the lungs with expansile pulsation seen nearly out to the periphery. It was on these findings that the diagnosis was made.

The film at 2 seconds shows the normal U-shaped curve of the right side of the heart and the aorta filling freely from the right ventricle, exactly in the position where the pulmonary artery should rise (Fig. 18). From 3 seconds onwards diodone is seen in the pulmonary arteries, though the lower part of the left ventricle is not seen till 4 seconds, having presumably filled through a ventricular septal defect.

The cardiac catheter passed easily from the right ventricle to the aorta, right subclavian, and common carotid. There seemed to be a left to right shunt, possibly as well as a right to left shunt through a high ventricular septal defect, as the oxygen saturation rose from 40 per cent in the right

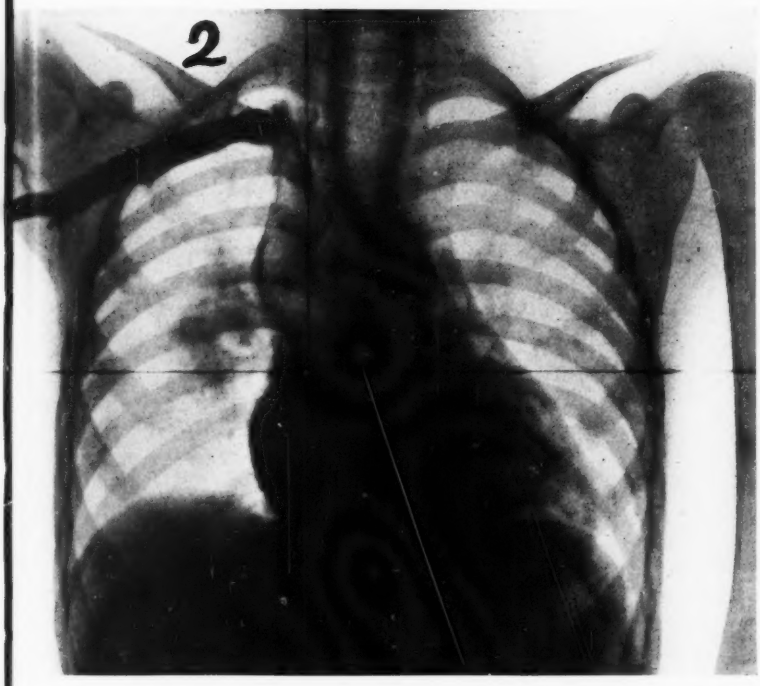
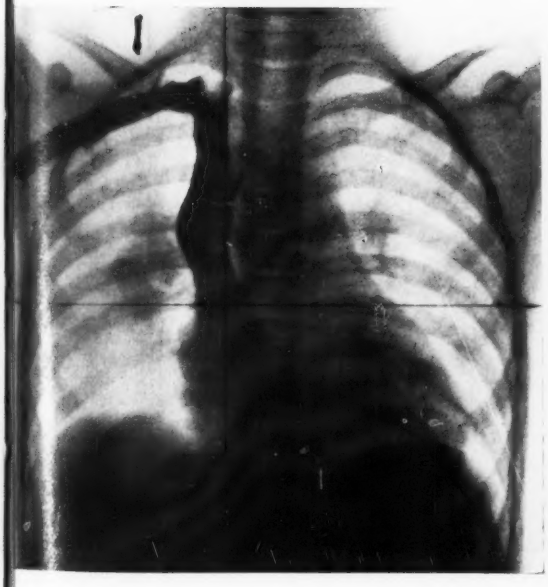


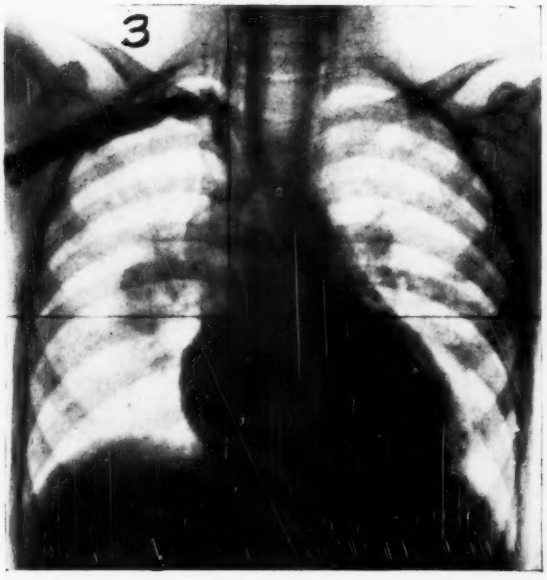
FIG. 18.—Complete transposition of the aorta and pulmonary artery.

(1) At 1 sec. there is diodone in the right auricle. There is an unusual indentation of the left side of the s.v.c., which later films show to be due to the dilated pulmonary artery instead of, as usual, the aorta. The P.A. is already visible in this first film because it was so dilated, but did not show more blood than in its normal resting condition.

(2) The film at 2 sec. (shown above and less reduced) shows the U-shape of the right side of the heart, with the aorta arising from this, as a direct continuation of the right ventricular outflow tract; the innominate and carotid arteries are well seen. There is no increase yet in the pulmonary shadows.

(3) At 3 sec. diodone has entered the left ventricle, probably through a ventricular septal defect, because of the clear space between the limbs of the U in the previous film. The lungs are now beginning to fill, and the aorta and its branches are still equally dense. Case 0052.





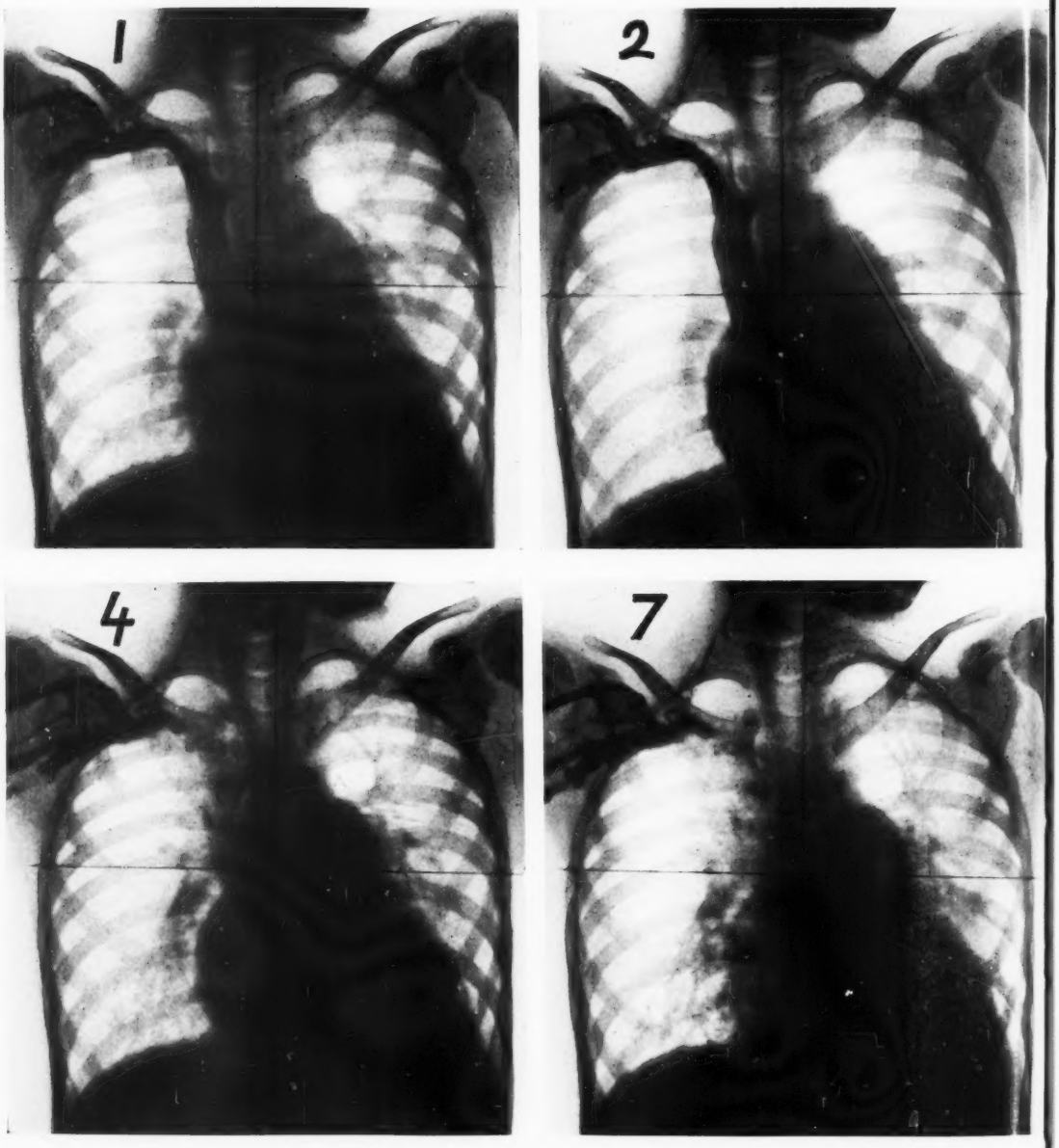


FIG. 19.—Partial transposition of the aorta and pulmonary artery.

(1) At 1 sec. there is some filling of the right auricle and ventricle.

(2) At 2 sec. there is more filling of the right ventricle and the aortic arch is already seen, though it appears more in the over-riding position than completely transposed, as it was in Fig. 18.

(4) At 4 sec. the aortic arch and its branches show clearly, and below this some filling of the pulmonary artery and its right branch. The left ventricle now seems well filled and the pulmonary artery may have filled entirely from this, though some degree of over-riding is difficult to exclude.

(7) At 7 sec. the shadow of the right auricle and the aorta (and probably the right ventricle) are fading, but there is no decrease in the density of the left ventricle or pulmonary artery and its branches. Case 0076.

auricle to 49·6 per cent in the right ventricle near the outflow tract, and to 52·8 per cent in the aorta. The pulmonary artery was not entered, which is not surprising if it arose from the left ventricle.

The diagnosis was complete transposition of the aorta and pulmonary artery with a ventricular septal defect, and possibly with an auricular septal defect also, though no direct evidence of this was obtained.

The second (Case 0076) had moderate cyanosis, and polycythæmia, the hæmoglobin being 122–130 per cent. He could sometimes walk half a mile. The heart was slightly enlarged (c.t.r., 11/20 cm.) and the pulmonary arteries were greatly dilated, with pulsation well seen out to the periphery.

On angiocardiography the aorta was seen at 2 seconds and better at 3 seconds (Fig. 19), but it was not very well filled and seemed to arise like an over-riding aorta and not wholly from the right ventricle as in the previous case. The pulmonary arteries were seen at the same time as the aorta, but though they were dilated the lungs filled slowly. If the pulmonary artery arises from the right ventricle it is difficult to reconcile this poor filling and the high degree of pulsation on screening, but if it arises from the left ventricle it would be expected, and there would be only slight early filling, either because the pulmonary artery over-rides the right ventricle slightly or because blood has passed from the right to the left ventricle through a septal defect.

Cardiac catheterization supported the clinical diagnosis and the final diagnosis was partial transposition of both aorta and pulmonary artery.

The first case is almost exactly the same as the one reported by Goodwin, Steiner, and Wayne (1949) and the teleradiograms are very similar (their Fig. 2 and Campbell, 1948, Fig. 12). Comparing this film with cardiac contours that Taussig thought characteristic of transposition they pointed out rightly that there were striking differences, especially in the broader pedicle. We think this contour most suggestive of transposition with a septal defect.

Eisenmenger's Complex

The remaining two were thought to have Eisenmenger's complex. A girl, aged 23, (Case 0261) had been fairly deeply cyanosed since she was three years old. She had not been able to play games at school because of dyspnœa, though she had been able to walk a mile at her own pace until the last two years. She had not squatted. Her colour was exceptionally high, the hæmoglobin being 160 per cent, and her fingers showed a moderate degree of clubbing.

She had a rough systolic murmur and thrill in the pulmonary area without any diastolic murmur, and the pulmonary sound was at the upper limits of normal. There was right ventricular preponderance in the electrocardiogram, confirmed by V leads, and also a very large pointed P in lead II.

Her heart was enlarged (c.t.r. 59, 11·9/20 c.m.). On screening the right ventricle was considerably enlarged in the oblique view, there was a large dilated pulmonary artery, enough to call aneurysmal, and pulsation could be seen out into the branches. The aortic arch was right-sided.

Cardiac catheterization helped to confirm this diagnosis. The pressure in the right ventricle was 95/5 and in the pulmonary artery 95/55 mm. Hg. against a systemic pressure of 130/80. The O_2 saturation was 77 per cent in the femoral artery, 62 per cent in the right ventricle, and 74 per cent in the pulmonary artery, suggesting a left to right shunt through the high ventricular septal defect, as there was no evidence of a patent ductus. The pulmonary and systemic blood flows were about the same and 70 per cent of the average normal, suggesting that the right to left and the left to right shunts were about equal.

If this diagnosis is right, and catheterization seems to prove it, this is one of the cases where the angiocardiogram is least helpful (Fig. 20). The aorta was never well defined and was missed at first, but could be seen faintly at 3 and 4 seconds and dye was seen in the subclavian from 6 seconds onwards, which is too early for its arrival by the normal circuit as the lungs did not

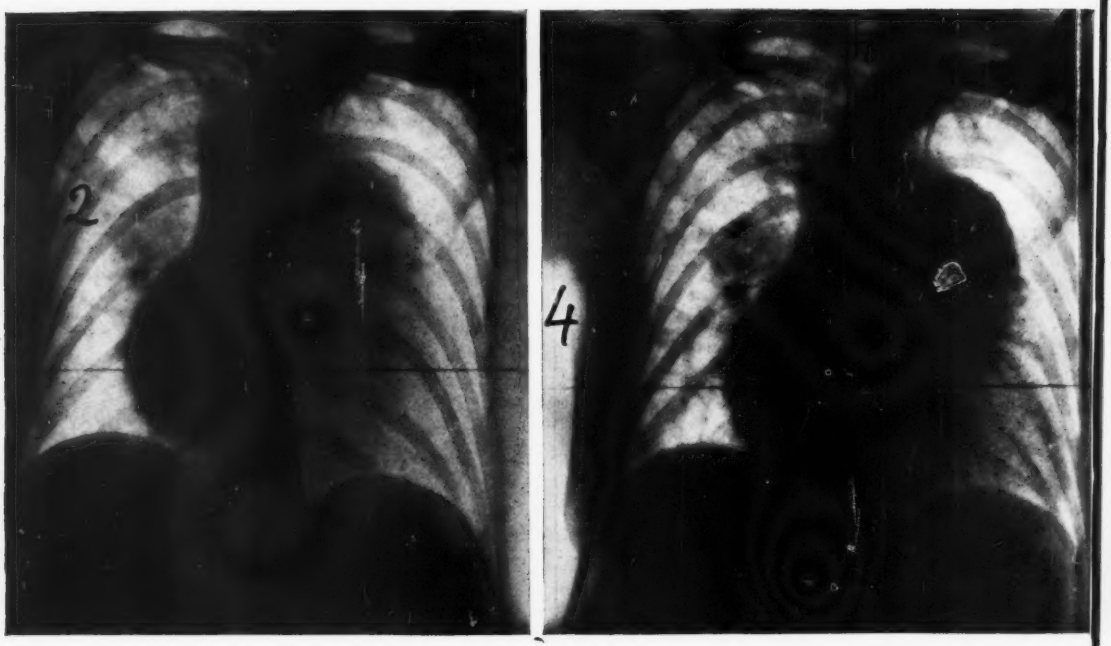


FIG. 20.—A large dilated pulmonary artery in Eisenmenger's complex.
(2) At 2 sec. diodone has reached the right auricle, but probably not much further, though the pulmonary artery is visible.
(4) At 4 sec. the large dilated pulmonary artery has filled completely and several branches in the lungs can be clearly seen. A small aortic knuckle is visible above this shadow, but considering her deep cyanosis the right to left shunt was not as great as expected. Case 0261.

fill quickly or well. There was, therefore, evidence of only a slight right to left shunt in spite of her low arterial saturation.

Nor were the findings in the pulmonary circulation as expected. The pulmonary artery, especially on the left side (but probably the main trunk), was grossly dilated and filled at 3 seconds. But it remained filled throughout and did not make the lungs much denser except in the right upper lobe, so that she was thought to have some diminution of the blood flow to the lungs (catheterization suggested 70 per cent of normal blood flow). It looks as if a dilated pulmonary artery and increased density of the lungs may sometimes be associated with more blood in the lungs rather than with increased flow.

The other (Case H126) had the main features of Fallot's tetralogy of moderate severity, but did not squat. The size of the heart (c.t.r. 66), some enlargement of the left ventricle as well as of the right on screening, and some possible left axis deviation in the standard leads, made us think tricuspid atresia possible, but the chest leads confirmed right ventricular preponderance. The inverted T in lead I might indicate an abnormal coronary artery arising from the pulmonary artery. The abnormal superior vena cava is shown in Fig. 2B.

The only certain features on angiocardiography were that she had a fairly large right to left shunt and that pulmonary stenosis was absent or trivial. It seems, therefore, that she had Eisenmenger's complex, or Fallot's tetralogy with relatively little stenosis and some complication, such as a single ventricle, producing the enlargement that seemed to affect both ventricles.

Abnormalities of the Veins

Apart from the main findings, several venous abnormalities of interest have been revealed by angiocardiography. In one patient there was a left superior vena cava; a smaller vessel could also be seen on the right, but seemed to taper off and it was doubtful if it entered the heart normally. Outside the left vena cava was another shadow that did not fill, so possibly the jugular vein ran down by the side of it, not communicating with it until almost in the heart (Fig. 2B).

In another diodone entered the right auricle by a superior vena cava that lay on the left (Fig. 10). Catheterization had already shown that the auricle could be entered through a right vena cava, but little dye crossed over to the other side, so it looked as if both these entered the auricle separately. Looking back at the straight X-ray film both superior venæ cavæ could be seen.

Fig. 21.—A complicated venous anastomosis in a patient who was thought to have arterio-venous aneurysms in various parts of the body. The film at 1 sec. shows this over the right chest well and no s.v.c. is really seen. Drainage seems to be to the azygos veins and the right side of the heart fills slowly. The speed with which the diodone is removed suggests a rapid blood flow.

In one cyanotic patient with a diagnosis of multiple arterio-venous aneurysms, not included in this series, there was a remarkable picture of anastomoses in the chest wall and no superior vena cava was clearly seen, so that diodone seemed to be reaching the heart through some anastomosis of the intercostal with the azygos veins (Fig. 21).

In another there was a large pulmonary artery on one side with obstruction on the other, shown post-mortem to be due to thrombosis in the pulmonary artery.

Summary and Conclusions

Angiocardiograms have been taken with a roll film camera at one second intervals by a method designed by Hills (1948). The small films cannot at present show the detail of a full-size film,

but facilitate serial comparison—a most important point in the diagnosis of congenital heart disease.

In severe cases of cyanotic heart disease angiocardiography is not without risk, and we have had two deaths in 70 cases. For children an anæsthetic is needed and whatever choice is made it should be given by an experienced anæsthetist with a liberal excess of oxygen. The first 15 minutes after angiocardiography is a dangerous period, so oxygen should be continued for at least 20 minutes even when the patient is safely back in bed.

The first film of the series will often show some venous backflow due to a temporary rise of venous pressure, often into the internal jugular vein or the inferior vena cava. This rise of pressure must be remembered, but rarely persists after two seconds, and does not seem to be the cause of the right to left shunt in any of this series.

In the first 50 cases of cyanotic congenital heart disease where angiocardiography has been carried out, 31 were thought to have Fallot's tetralogy. The volume of the right to left shunt is estimated mainly by the proportion of diodone in the aorta, which is seen as early as two or three seconds after the injection. The filling of the subclavian and other systemic arteries gives further evidence of the amount taking this route.

The pulmonary arteries show some filling at two seconds, but the degree of stenosis should not be assessed on a time basis alone. If there is a normal blood flow through the lungs their general density will increase to a maximum in 2 or 3 seconds; if there is pulmonary stenosis, in 4 to 6 seconds, or less if a grossly over-riding aorta carries away most of the diodone. The changing density of the lung fields is a better guide than the time of arrival or the degree of filling of the main arteries, which may be dilated.

In all these 31 cases there was a right to left shunt and in all but one it was large and easily seen. In 25, angiocardiography showed moderate or severe pulmonary stenosis: in 6 it seemed slighter, and this led to some doubt about their suitability for the Blalock-Taussig operation, which was, however, as successful as in the others.

One case resembled Fallot's tetralogy in some but not in all features, and proved post-mortem to have pulmonary atresia.

There were 5 others where the picture was of Fallot's tetralogy with the addition of signs of patent ductus arteriosus. In one, this diagnosis was supported by operation. In another, necropsy showed that there was, in fact, complete pulmonary atresia with a patent ductus, and some at least of the others were thought to have pulmonary atresia, or perhaps in one case a common arterial trunk, with the pulmonary blood supply through bronchial arteries.

There were 2 cases where the clinical diagnosis was tricuspid atresia with a non-functioning right ventricle, and in these there was confirmatory evidence, the aorta filling a little later and apparently from the right auricle through an auricular septal defect to the left auricle and so to the left ventricle and aorta.

There were 7 cases where the clinical diagnosis was pulmonary valvular stenosis without a ventricular septal defect, but sometimes with a patent foramen ovale. In three of these there was no evidence of any shunt (though in one we think it must have been present) and in one, who was acyanotic, the absence of a septal defect was confirmed post-mortem. In the other four there was thought to be a right to left shunt through a patent foramen ovale, and in three of these it was confirmed post-mortem.

In 2 the diagnosis was thought to be Eisenmenger's complex: in one of these there was good evidence to support this on cardiac catheterization, but less decisive evidence from angiocardiography.

In the last two cases the clinical diagnosis was transposition of the aorta and pulmonary artery with septal defect; supporting evidence was found from angiocardiography and cardiac catheterization though in the second it was not conclusive and the transposition was probably partial.

Of these 50 cases, 48 were cyanotic and all these, except one, had evidence of a right to left shunt, though in three it was slight and not easily seen. In the one exception, who had been moderately

cyanosed since he was nine months old, catheterization suggested a right to left shunt, and we think the angiocardiogram failed to demonstrate it.

Of the two acyanotic cases, neither had evidence of a right to left shunt, and in one the absence of any septal defect was confirmed post-mortem. A right to left shunt was, therefore, present in 47 cases. In 36 it was thought to be due to an over-riding aorta, probably with a high ventricular septal defect, and in one other this was difficult to exclude. In 4 it was not certain where the right to left shunt was.

In the remaining 7 it was through an opening in the auricular septum. In 3 of these, two with tricuspid atresia and one with pulmonary atresia, it was through a true auricular septal defect (one proved post-mortem): the upper border of the left auricle was generally seen very clearly. In 4 with pulmonary valvular stenosis it was through a patent foramen ovale (three proved post-mortem), and in these the evidence of the right to left shunt was often less well seen. This might be expected when only a small proportion of the blood is passing through a small patency of the foramen ovale, instead of the whole of it through an auricular septal defect because there is no direct way from the right auricle to the right ventricle.

Unsuspected abnormalities, such as a double superior vena cava were sometimes found.

We have discussed the angiocardiograms mainly from the point of view of diagnosis, but in cases for operation the detailed picture of the anatomy of the arteries is of value to the surgeon in deciding if and how a subclavian-pulmonary anastomosis should be attempted, and may help in deciding if a Blalock-Taussig operation or Brock's direct attack on the obstruction is indicated.

We are greatly indebted to Dr. Ian Hill for giving most of the injections for these angiocardiograms and to Dr. E. H. Rink for giving many of the anæsthetics and for his help in the section about this. We should like to thank our fellow members of the Peacock Club for many discussions on these films from time to time, and especially Mr. R. C. Brock. We should also like to thank Dr. Frances Gardner for her useful suggestions, Dr. Charles Baker for the use of some of his cases, and Dr. Holling and Dr. Zak for their results of cardiac catheterization.

The Photographic Department, Guy's Hospital have helped us with the illustrations.

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ABSTRACTS OF CARDIOLOGY

The Effects of Dicumarol on the Electrocardiogram. S. S. BALKIN and A. GOOTNICK. *J. Lab. clin. Med.*, **33**, 972–974, Aug., 1948.

Leads I, II, III, CF2, CF4, and CF5 were used for electrocardiography, and 48 patients were divided into four groups: (1) 12 with no evidence of cardiovascular disease; (2) 16 with various types of cardiovascular disease other than infarction; (3) 14 with acute infarction; (4) those whose cardiograms showed a digitalis effect. In groups 1 and 2 all cardiograms taken at successively lower prothrombin levels were substantially the same. An occasional tracing showed minimal changes in amplitude of the T wave in lead I, and more rarely in the amplitude of the P wave, commensurate with the associated changes in rate. In group 3 the expected progressive changes of healing infarction were observed, and the rate of progress did not differ materially from that obtained in patients not receiving dicoumarol. Withdrawal of the drug during convalescence did not cause significant cardiographic change. All tracings in group 4 retained patterns which were unchanged by effective doses of dicoumarol. It is concluded that in none of the four groups of subjects was significant electrocardiogram deviation attributable to dicoumarol. *S. Oram*

Electrocardiographic Changes in Diabetics after Physical Stress. S. I. KALYAEVA and R. D. DIBNER. *Klin. Med., Mosk.*, **26**, No. 5, 79–82, May, 1948.

Diabetics develop arteriosclerosis early, amongst other sites in the coronary arteries. Anichkov ascribes this to a disturbance of the cholesterol metabolism.

The authors have aimed at estimating the functional capacity of the coronary arteries of patients up to 50 years of age with glycosuria. They chose the electrocardiographic method, taking records during rest and immediately after physical exertion. This last consisted of walking up a three-step ladder (presumably revolving) to a distance equivalent to a climb to the third floor of the Institute. Twenty-eight patients were examined, 5 with diabetes of mild, 14 of medium, and 9 of marked severity; there were 22 controls. In 26 there were no clinical signs of cardiovascular changes; 2 had hypertension. The electrocardiograms before exercise were normal in 14 cases; there was left axis deviation in 9 (including the 2 with hypertension) and right axis deviation in 2. The remaining 3 showed slight depression of the ST portion in leads I and II. The control group were all normal, clinically and cardiographically.

After the patients' exercise, 9 electrocardiograms showed changes corresponding to coronary insufficiency (depression of ST in leads I and II), but there were no changes in controls. Other alterations in the cardiogram, such as changes in height of the T wave, with depression of the PQ segment, were observed with equal frequency in diabetic and control subjects. The authors conclude that in diabetes mellitus there is an especial tendency to early coronary changes.

L. Firman-Edwards

Alterations of Radial or Brachial Intra-arterial Blood Pressure and of the Electrocardiogram Induced by Tilting. R. S. GREEN, A. IGLAUER, and J. MCGUIRE. *J. Lab. clin. Med.*, **33**, 951–960, Aug., 1948.

The effect on the heart rate and blood pressure of tilting normal subjects was studied. Previous investigations have yielded widely divergent findings, which, the authors state, are due to the fact that it is impossible to obtain accurate readings of a rapidly changing blood pressure with an ordinary sphygmomanometer, and because the position of the arm during the tilting has varied in different experiments.

They recorded the intra-arterial blood pressure by means of a needle within the brachial artery at the elbow or radial artery at the wrist. The arm was maintained in a horizontal plane. Tilting was controlled by an electrically operated table, the subjects being supported so that muscular activity was not required to maintain the position. They were tilted head down to 45 degrees and erect to 20 degrees " at a moderate rate." An electrocardiogram was used to record the heart rate.

Blood pressure rose immediately in all subjects during the tilt from 20 degrees erect to 45 degrees head down, and fell immediately during the return tilt. In the 15 healthy young adults investigated these primary alterations of blood pressure were followed by a characteristic pattern of depressor response in the head down position, and of pressor response in the erect position, whereby the blood pressure returned in from 8 to 18 seconds to a level that was approximately the same regardless of the position of the body. The heart rate always slowed in the head down position and increased in the erect position. In some subjects, whilst in the head down position, the P wave gradually decreased in size and finally disappeared for several beats. The authors consider that, as these changes were not associated with shortening of the P–R interval, the resultant rhythm was not nodal. *S. Oram*

Pharmacology of the Failing Human Heart. J. MCMICHAEL. *Brit. med. J.*, **2**, 927–933, Nov. 27, 1948.

The author describes the pharmacological actions of digoxin, g-strophanthin (ouabain), theophylline, and mersalyl on the failing human heart. Forssmann's technique of right-hand catheterization was used in observing the action of digoxin and g-strophanthin.

Generalized venous congestion is seen in conditions that demand an increase in cardiac output as well as

in conditions which impair the cardiac mechanism and thus reduce its output. The former is regarded as compensatory to maintain the increased flow. On this basis the author classifies the congestive type of heart failure into two groups: (*a*) failure with high output due to conditions demanding an increase in the output, such as anæmia, emphysema, Paget's disease, and metabolic disturbances; and (*b*) failure with low output due to ischæmia, hypertensive and valvular heart disease. In both groups the venous pressure is high, and the author believes that digoxin produces its beneficial effects by lowering this pressure. He states that, whereas in the first group this reduction in pressure causes diminution in cardiac output, in the second group it increases it. Unlike g-strophanthin, digoxin is said to have insignificant action on the failing myocardium, and its hitherto well-known rate-reducing action is regarded only as an excellent guide to proper maintenance dosage when the drug is given over a long period of time. Experimental evidence is offered in support of these conclusions.

Theophylline is considered to have a direct stimulating action on the healthy heart as well as on the failing heart, increasing the cardiac output and thus reducing the venous pressure. This increased activity of the heart also produces secondary coronary dilatation, and the author adds timely warning as to the indiscriminate use of this drug in coronary thrombosis. Finally, observations made by his colleagues on the circulatory action of mersalyl are quoted. It is thought that mersalyl, by producing diuresis, reduces the venous pressure and thus raises the cardiac output. This action is similar to that of a venesection. *S. Karani*

Renal and Circulatory Factors in the Edema Formation of Congestive Heart Failure. A. P. BRIGGS, D. M. FOWELL, W. F. HAMILTON, J. W. REMINGTON, N. C. WHEELER, and J. A. WINSLOW. *J. clin. Invest.*, **27**, 810–817, Nov., 1948.

Twenty-one cases of congestive heart failure were extensively studied and compared with 18 cases of heart disease without failure. In 10 of the cases with failure it was possible to repeat the studies after compensation had been restored. The glomerular filtration rate was found to be decreased in the cases of failure, but it did not always increase significantly as the œdema disappeared, whereas the ability to excrete sodium invariably increased. The authors conclude that some factor connected with the heart failure is present which forces the kidney to resorb sodium and water more completely than normal. Of the circulatory measurements the only one that showed a fairly consistent difference between the two groups was the oxygen saturation of the mixed venous blood. In most instances this was lower in the uncompensated cases and improved with compensation. The authors suggest that this indicates cellular hypoxia, which, acting possibly through the posterior pituitary or the suprarenals, causes the kidney to resorb sodium and water more completely with resultant œdema formation. Once established, increased capillary hydrostatic pressure and lowered plasma proteins may maintain or perhaps increase the œdema. *B. McArdle*

The Effects of the Cardiac Glycosides upon the Dynamics of the Circulation in Congestive Heart Failure. I. Ouabain. R. A. BLOOMFIELD, B. RAPOPORT, J. P. MILNOR, W. K. LONG, J. G. MEBANE, and L. B. ELLIS. *J. clin. Invest.*, **27**, 588–599, Sept., 1948.

The object of this study was, by means of certain newer techniques, to gain further insight into the action of ouabain. Thirteen patients with heart disease, with and without clinical evidence of congestive heart failure, were investigated. Ouabain was injected through an intracardiac catheter into the right ventricle or pulmonary artery, over a period of one to two minutes, in doses of 0·25 to 0·75 mg. and the cardiac output was estimated before and afterwards by the direct Fick method. Intracardiac, femoral arterial, and peripheral venous pressures were optically recorded.

The authors' main conclusions were that the cardiac output was increased in heart failure owing to the fact that ouabain causes an increase in the stroke volume, and that this greater stroke volume could best be explained by a direct action on the contractility of the myocardium. *S. Oram*

Paradoxical Behaviour of the Electrocardiogram after Effort in Patients with Coronary Insufficiency. A. MUSSAFIA. *Cardiologia, Basel*, **13**, 212–225, 1948.

Amongst about 1000 patients in whom 2 or 3 electrocardiograms were taken after exercise (Master's two-step test) paradoxical changes were found in 35. In 16 of these an electrocardiogram abnormal at rest became normal in all leads after exercise, in 14 the abnormalities became less pronounced but did not entirely disappear in any or certain leads, and in 5 an improvement was found in some and deterioration in other leads; 28 patients had angina pectoris (in 10 of these pain occurred during the exercise test) and, of the remaining 7, 5 had valvular lesions and 2 arteriosclerosis. The improvement in the electrocardiogram may be only apparent; the changes may be due to the effect of extracardiac nerves or they may be due to an improvement, due to exercise, of the circulation through small vessels of the heart. The first 2 of these possibilities are rejected; the last one is discussed in more detail, also in relation to the mechanism precipitating anginal pain. [This explanation is highly hypothetical and not entirely convincing.] *A. Schott*

Production of Experimental Heart Failure in Dogs with Intact Circulation. A. ROOS and J. R. SMITH. *Amer. J. Physiol.*, **153**, 558–566, June, 1948.

Heart failure was produced in dogs by injection into the left ventricle of a 3·3% suspension of potato starch in saline, the aorta being occluded immediately above the heart for a few seconds during the injection. This produced diffuse myocardial damage by coronary embolism, most of the injected small (diameter 12 to 72 μ) particles presumably getting into the coronary arteries. The injections were repeated at 2 to 7 minute intervals. After more than three injections myocardial

failure was produced in most dogs, as evidenced first by a progressive rise in right auricular pressure, then by dilatation of the heart, congestion of the lungs and liver, and pulmonary œdema. The arterial pressure did not fall significantly until congestive heart failure had fully developed. The experiments usually terminated in death. Congestive failure could generally be produced with less starch suspension when the blood volume was first increased by 100 to 250 ml. of blood. In a few animals congestive heart failure did not develop but a precipitous fall in arterial blood pressure occurred, leading to death.

It is noted that whereas in the experiments of Landis *et al.* coronary ligation alone (without "exercise") produced a fall in venous pressure, coronary embolism in the present experiments produced a progressive rise in pressure. There is a discussion on the changes in cardiac output in relation to right auricular pressure.

H. Pollak

Some Observations on the Cardiac Output and its Measurement, with a Description of a Modified Carbon Dioxide Method. M. J. MORRISSEY and A. J. PALMER. *Med. J. Aust.*, **1**, 113–118, Jan. 29, 1949.

This paper contains a description of a modification of the technique for measurement of the cardiac output with the Fick formula and the carbon-dioxide method of Douglas and Haldane. The apparatus was devised to render the results independent of the co-operation of the subject tested. It enables the operator to conduct the measurement at a distance. Even so, this apparatus does not eliminate all sources of possible errors inherent in the carbon-dioxide method itself. In 12 normal subjects under basal conditions the cardiac output varied from 3·4 to 7 litres per minute, and the cardiac index from 2 to 3·7. *A. I. Suchett-Kaye*

The Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defects on the Development of Pulmonary Vascular Lesions. K. J. WELCH and T. D. KINNEY. *Amer. J. Path.*, **24**, 729–761, July, 1948.

This investigation was undertaken to obtain some idea of the ultimate effects of anastomosing a systemic to a pulmonary artery as in the operative treatment of pulmonary stenosis. In necropsies on 67 cases with congenital systemic→pulmonary shunts of various kinds atherosclerosis was greater than in the controls in only 11 cases, and in 9 of these the increase was probably due to rheumatic mitral disease. *D. M. Pryce*

Clinical Observations on Cardiac Dynamics in Healthy Subjects. H. REINDELL and L. DELIUS. *Dtsch. Arch. klin. Med.*, **193**, 639–655, 1948.

From kymographic and hæmodynamic findings the authors estimate that in the heart of normal subjects the residual blood volume is about double the stroke volume; in highly trained subjects the amount of residual blood is further increased. The increase in the stroke volume after exercise is associated with a decrease in cardiac volume (estimated radiologically) and is at least partly due to a decrease in the residual blood volume. The inhibitory vagal and stimulating sympathetic effects upon cardiac work are relatively independent of the cardiac volume. It is pointed out that, as a result of sympathetic nervous action, additional energy can be utilized by a mechanism which is independent of length or tension of fibres. The vagal effect, on the other hand, results in increased economy of the cardiac mechanism.

A. Schott

Ventricular Septal Defect and Pulmonary Hypertension without Hypoxemia. H. B. BURCHELL, B. E. TAYLOR, A. A. POLLACK, J. W. DUSHANE, and E. H. WOOD. *Proc. Mayo Clin.*, **23**, 507–410, Oct. 27, 1948.

In the study of a case of ventricular septal defect with a large left to right shunt and normal arterial oxygen saturation but a marked pulmonary hypertension, cardiac catheterization is employed to illustrate a possible relation between isolated ventricular septal defect occurring in early life and a subsequent fully developed Eisenmenger complex. *J. L. Lovibond*

Renal Function Before and After Surgical Resection of Coarctation of the Aorta. J. GENEST, E. V. NEWMAN, A. A. KATTUS, B. SINCLAIR-SMITH, and A. GENECIN. *Bull. Johns Hopk. Hosp.*, **83**, 429–438, Nov., 1948.

Twelve out of 17 patients suffering from coarctation of the aorta were investigated before and after operation to determine the renal filtration rate, the renal plasma flow, and the filtration fraction. In most of the cases the successful resection of the constriction and the end-to-end anastomosis produced an increase in the renal blood flow and a decrease of the filtration fraction. The authors believe that the diminished renal blood-flow with nearly normal filtration rate in patients with coarctation of the aorta is due to a compensatory efferent arteriolar constriction—a physiological mechanism similar to that present in essential hypertension. The successful operation of the coarctation releases the constriction of the efferent artery. *A. I. Suchett-Kaye*

Diffuse Interstitial Myocarditis in Children. R. K. HOUSE. *Amer. J. Pathol.*, **24**, 1235–1257, Nov., 1948.

Most of the reported cases of Fiedler's myocarditis have been in adults. The disease occurs in children also, and 4 such cases, in patients whose ages ranged from 3 weeks to 13 months, are described. The myocardial lesions were acute in 3 cases and more chronic in the fourth. Histologically the change was inflammatory and had no specific features. Concurrent necrosis and disappearance of muscle fibres were seen. Endocardium and pericardium were unaffected, or only secondarily involved over the area of the muscle lesion. Terminal pneumonia was present in all 4 cases. *L. Crome*

The Prognosis in Myocardial Infarction. I. The Prognosis After the Acute Stage. Study of 100 Cases. A. MUSSAFIA and V. MASINI. *Cuore e Circol.*, **32**, 193–200, Aug., 1948.

A series of 100 patients who survived the acute stage of myocardial infarction was followed up. The patients could be divided into three groups: (*a*) Those who made a good functional recovery, without angina or cardiac failure. There were 3 women and 54 men in this group, and the ages ranged from 30 to 72 years, with an average of 50 years. In 32 patients hypertension, and in 25 angina, preceded the attacks. Five of the patients died, a new infarct being the cause in 4. (*b*) Those who suffered from angina following the infarct. In this group were 22 men and 1 woman; the ages ranged from 34 to 72 years, with an average of 49·5 years. Hypertension preceded the infarction in 15 cases, angina in 18 (in 10 associated with hypertension), and cardiac failure in 1 (associated with hypertension). Four patients died while under observation, a further infarct being the cause of death of 2 of them. (*c*) Patients with subsequent cardiac failure. In this group there were 2 women and 18 men, whose ages ranged from 48 to 65 years, with an average of 56·3 years. Hypertension preceded the attack in 16 patients, angina in 10 (of which 9 had associated hypertension), and cardiac failure in 7 (all associated with hypertension). Seven patients subsequently died of cardiac failure, but none had a further infarction during the period of observation.

Many patients survived the original infarction for more than 8 years. Causes of death were cardiac failure or coronary insufficiency (usually a further infarction). Cardiac failure was more common when hypertension preceded infarction. Recurrence of infarction was unpredictable, and occurred in patients of the first group many years after the first attack. *F. A. Langley*

Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. (A Progress Report on the Statistical Analysis of the First 800 Cases Studied by This Committee). I. S. WRIGHT, C. D. MARPLE, and D. F. BECK. *Amer. Heart J.*, **36**, 801–815, Dec., 1948.

The authors have analysed the records of 800 cases of coronary thrombosis treated in 16 hospitals by members of a committee, set up by the American Heart Association. Of this total, 368 patients were treated conventionally, the remaining 432 being treated, in addition, with anticoagulants along the following lines. Heparin was given for the first 48 hours or more if desired. Dicoumarol, 200 to 300 mg. daily, was given until the prothrombin time was 30 seconds, then 40 to 100 mg. daily if the prothrombin time was between 30 and 35 seconds. When the prothrombin time was 35 seconds or longer, dicoumarol was withheld until it had fallen to 30 seconds or under, when the drug was again given cautiously in 100 mg. doses. Prothrombin time was estimated daily by the Link-Shapiro technique or by the Quick method. Treatment was continued for at least 30 days and preferably for 30 days after the last thromboembolic episode, unless contraindicated. The cases in the two groups were unselected and comparable. Of the control group 23%, and of the treated group 30% were classified as having severe attacks.

Mortality in the control group was 24%, and in the treated group 15%—a statistically significant difference. The lower death rate in the treated group was largely due to the lower incidence of thrombo-embolic complications, which occurred in 25% of controls and in only 11% of treated patients; in 5% of the latter group the episode occurred before treatment began or within the first 3 days of anticoagulant treatment. The death rate by age group, the incidence and site of embolism, and the complications due to treatment are analysed.

D. Verel

The Prognosis in Myocardial Infarction. II. Prognosis in Relation to the Electrocardiographic Type and to its Evolution. Study of 100 Cases. V. MASINI and A. MUSSAFIA. *Cuore e Circol.*, **32**, 253–261, Oct., 1948.

The authors studied serial electrocardiograms in 100 cases of myocardial infarction, and attempted to relate prognosis to the progressive electrocardiographic changes. They conclude that the position of the myocardial infarct is of little prognostic significance. Of greater importance is the extent, the larger the infarct the worse being the prognosis. Associated changes in the electrocardiogram, such as low-voltage curves, bundle-branch block and arrhythmias, did not materially worsen prognosis. In patients who made a good clinical recovery a larger proportion of electrocardiograms became normal. However, no close relation between clinical progress and serial electrocardiographic changes could be conclusively demonstrated. *E. G. Sita-Lumsden*

Physiological Studies in Congenital Heart Disease. VII. Pulmonary Arterial Hypertension in Congenital Heart Disease. H. E. GRISWOLD, R. J. BING, J. C. HANDELSMAN, J. A. CAMPBELL, and E. LEBRUN. *Bull. Johns Hopk. Hosp.*, **84**, 76–88, Jan., 1949.

This deals with the occurrence of arterial pulmonary hypertension in a series of cases comprising 8 patients with ventricular septal defect, 5 with auricular septal defect, 2 with patent ductus arteriosus, 6 with coarctation of the aorta, and 3 with partial transposition of the great vessels. Direct measurement of pressures in the pulmonary artery by means of an intracardiac catheter gave mean values ranging from 25 to 102 mm. of Hg. There are three possible mechanisms that could operate to produce this rise in arterial pulmonary pressure: (1) Increase in pulmonary blood flow exceeding the functional capacity of the left auricle; (2) increase in left auricular pressure; and (3) increase in pulmonary peripheral arterial resistance; in 2 illustrative cases there was a large overall right-to-left intracardiac shunt. This increase in pulmonary peripheral arterial resistance has been found to be due in some cases to functional and in others to arteriolosclerotic changes in the pulmonary vessels. *A. I. Suchett-Kaye*

The Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort. W. B. PORTER. *Amer. J. med. Sci.*, **216**, 509–515, Nov., 1948.

Four patients with angina pectoris and normal electrocardiograms at rest developed frequent premature ventricular systole immediately following an exercise test. After treatment with quinidine, 0·3 g. thrice daily, the effort tolerance increased and no premature systoles occurred during the exercise test. Two of the 4 patients died soon afterwards, and it is suggested that premature systoles occurring during the tachycardia induced by exercise have a grave prognostic significance. Since death is probably due to ventricular fibrillation in these patients, it seems reasonable to give them quinidine.

C. W. C. Bain

The Characteristics of a Resistance-wire Manometer for Measuring Blood Pressure in Cardiac Catheterization Studies. E. H. LAMBERT and R. E. JONES. *Proc. Mayo Clin.*, **23**, 487–493, Oct. 27, 1948.

The different principles of pressure recording in catheterization of the heart are discussed. Resistance-wire manometers have certain advantages over the other methods and have shown their instrumental superiority both in static and dynamic tests. *J. L. Lovibond*

The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale. A. SELZER, W. H. CARNES, C. A. NOBLE, W. H. HIGGINS, and R. O. HOLMES. *Amer. J. Med.*, **6**, 3–23, Jan., 1949.

The authors claim that this syndrome should be recognized clinically. They describe 2 personal cases in detail and give the findings in 27 reported cases.

Its characteristics are contrasted with those of pulmonary stenosis without septal defects, Fallot's tetralogy, and Eisenmenger's complex. The syndrome of pulmonary stenosis with patent foramen ovale belongs to the cyanotic group of cardiac abnormalities. The cyanosis, due to a right-to-left shunt, is usually less severe than in the tetralogy of Fallot but more pronounced than in Eisenmenger's syndrome; pulmonary stenosis with closed septa is essentially a non-cyanotic disease. Other features of the syndrome are polycythæmia, clubbing, systolic murmur at the pulmonary area, second pulmonary sound decreased or absent; radiological investigation shows dilatation of the pulmonary artery but without hilar pulsation. Electrocardiography reveals right ventricular hypertrophy, prominent P waves, and occasionally right bundle-branch block due to hypertrophied right ventricle.

The main interest of this clinical identification of the syndrome of pulmonary stenosis with patent foramen ovale lies in the fact that in cases of this cardiac defect benefit may be expected from surgical intervention.

A. I. Suchett-Kaye

Angiocardiography in Coarctation of the Aorta. E. F. SALÉN and T. WIKLUND. *Acta radiol., Stockh.*, **30**, 299–315, 1948.

In 14 cases of coarctation of the aorta angiocardiography was performed. Of these 11 were operated upon and in 6 post-operative angiocardiograms were taken. Robb and Steinberg's technique was used; 50 ml. of 70% diodone was injected into the cubital vein in 2 seconds. All patients were tested beforehand for iodine-sensitivity, either by the skin test or by an intravenous injection of 2 ml. of the contrast medium. Two cases were rejected on these grounds. A serial cassette changer capable of holding 6 cassettes was used, and films could be taken at the rate of almost one per second. The arm-to-tongue circulation time was estimated first, and in most cases the initial film was taken at the number of seconds after injection corresponding to half the circulation time; subsequent exposures were made at intervals of 1 to 2 seconds.

The main features searched for in the radiographs were: (1) the location of the stenosis relative to the left subclavian artery; (2) the length of the stenosed portion; and (3) the degree of the stenosis. Post-operative angiocardiograms were found useful in assessing the results. It was noted that the lumen of the stenosed part of the aorta was never restored to normal, but was usually very much enlarged. *J. W. D. Bull*

Notching of Ribs Without Coarctation. P. BATCHELDER and R. J. WILLIAMS. *Radiology*, **51**, 826–830, Dec., 1948.

The authors report a case in which there was notching of the left 5th, 6th, 7th, and 8th ribs in the absence of coarctation of the aorta, associated with Fallot's tetralogy and cystic disease in the left upper lobe. Histological study of the affected arteries revealed no evidence of congenital weakness or developmental anomaly to account for the unusual distribution. *L. G. Blair*

Familial Interauricular Septal Defect with Mitral Stenosis (Lutembacher's Syndrome). S. R. COURTER, B. FELSON, and J. MCGUIRE. *Amer. J. med. Sci.*, **216**, 501–508, Nov., 1948.

Two sisters aged 21 and 25 years with Lutembacher's syndrome are reported; no previous report of this syndrome in brothers or sisters has been found up to 1947. Fifty-four cases of Lutembacher's syndrome have been reported.

The history and physical findings are described and radiographs, electrocardiograms, and phonocardiograms reproduced. Criteria for the diagnosis are mentioned. Fluoroscopy should show signs of: (1) generalized enlargement of the right heart; (2) marked prominence of the pulmonary conus; (3) increased hilar markings with "hilar dance"; (4) a small left ventricle; (5) a hypoplastic aorta. To these signs are added a characteristic apical diastolic murmur to complete the findings in the syndrome. *John Anderson*